

Treatment for Bipolar Disorder in Adults: A Systematic Review

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Treatment for Bipolar Disorder in Adults: A Systematic Review

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Key Messages

Purpose of Review

- To assess the effectiveness of drug and nondrug therapies for treating acute mania or depression symptoms and preventing relapse in adults with bipolar disorder (BD) diagnoses, including bipolar I disorder (BD-I), bipolar II disorder (BD-II), and other types.

Key Messages

- Acute mania treatment: Lithium, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone may modestly improve acute mania symptoms in adults with BD-I. Participants on atypical antipsychotics, except for quetiapine, reported more extrapyramidal symptoms, and those on olanzapine reported more weight gain, compared with placebo.
- Maintenance treatment: Lithium may prevent relapse into acute episodes in adults with BD-I.
- Depression treatment: Evidence was insufficient for drug treatments for depressive episodes in adults with BD-I and BD-II.
- For adults with any BD type, cognitive behavioral therapy may be no better than other psychotherapies for improving acute bipolar symptoms and systematic/collaborative care may be no better than other behavioral therapies for preventing relapse of any acute symptoms.
- Stronger conclusions were prevented by high rates of participants dropping out.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

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If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Treatment for Bipolar Disorder in Adults: A Systematic Review

Structured Abstract

Objective. Assess the effect of drug and nondrug interventions for treating acute symptoms associated with bipolar disorder (BD) and preventing relapse.

Data sources. Ovid MEDLINE® and PsycINFO®, the Cochrane Central Register of Controlled Trials, and Ovid Embase® bibliographic databases; hand searches of references of relevant systematic reviews through May 2017.

Review methods. Eligible studies included randomized controlled trials and prospective cohorts with comparator arms enrolling adults with bipolar disorder (BD) of any type with 3 weeks followup for acute mania, 3 months for depression, and 6 months for maintenance treatments. We excluded acute mania and depression studies with greater than 50 percent attrition.

Results. We synthesized evidence from 157 unique studies, 108 studies for 28 drugs, 49 studies for nondrug interventions. All drug study findings with at least low-strength evidence were based almost exclusively on adults with bipolar I disorder (BD-I). Asenapine, cariprazine, quetiapine, and olanzapine improved acute mania symptoms compared to placebo (low-strength evidence). However, improvements were of modest clinical significance, with values that were less than the minimally important difference, but still large enough that a reasonable proportion of participants likely received a benefit. Unpooled evidence indicated an overall beneficial effect of risperidone and ziprasidone on acute mania symptoms compared to placebo (low-strength evidence). Participants using atypical antipsychotics, except quetiapine, reported more extrapyramidal symptoms compared to placebo, and those using olanzapine reported more clinically significant weight gain. Lithium improved acute mania in the short term and prolonged time to relapse in the long term compared to placebo (low-strength evidence). No difference was found between olanzapine and divalproex/valproate for acute mania (low-strength evidence). For drugs not approved for BD, paliperidone improved acute mania compared to placebo (low-strength evidence), while topiramate and allopurinol showed no benefit (low-strength evidence). Further, lithium improved acute mania better than topiramate (low-strength evidence), although withdrawals for adverse events were lower for topiramate. Only lithium reached a minimally important difference for acute mania and maintenance treatment. All other drug comparisons to placebo or active controls for acute mania, depression, and maintenance had insufficient evidence. For psychosocial interventions, cognitive behavioral training (CBT) was no better for depression or mania symptoms than psychoeducation or other active psychosocial comparators (low-strength evidence). Systematic/collaborative care had no effect on relapse compared to inactive comparators (low-strength evidence).

Conclusions. We found no high- or moderate-strength evidence for any intervention to effectively treat any phase of any type of BD versus placebo or an active comparator. All antipsychotics approved by the Food and Drug Administration, except aripiprazole, had low-strength evidence for benefit for acute mania in adults with BD-I. Lithium improved short-term for acute mania and resulted in longer time to relapse in the long term versus placebo in adults

with BD-I. Aside from low-strength evidence showing CBT and systematic/collaborative care having no benefit for a few outcomes, evidence was insufficient for nondrug interventions. Information on harms was limited across all studies. Future research examining BD treatments will require innovative ways to increase study completion rates.

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Evidence Summary

Background

Bipolar disorder (BD), also known as manic-depressive illness, is a serious mental illness that causes unusual shifts in mood, energy, activity levels, and the inability to carry out day-to-day tasks. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) recognizes a spectrum of bipolar diagnoses that differ in duration of bipolar episodes/periods and impairment: bipolar I disorder (BD-I), bipolar II disorder (BD-II), BD otherwise specified, and BD unspecified. Prevalence studies estimate about 1 percent of the population for BD-I, another 1 percent for BD-II, and up to 5 percent for the full spectrum of BD diagnoses, with relatively similar prevalence in men and women and across cultural and ethnic groups.^{1, 2} BD represents a significant individual and societal burden. Recurrent episodes of mania and depression can cause serious impairments in functioning, such as erratic work performance, increased divorce rates, and psychosocial morbidity.^{3, 4} People with bipolar disorder account for between 3 and 14 percent of all suicides, and about 25 percent of bipolar disorder patients will attempt suicide.⁵ Further adding to the individual illness burden, 92 percent of individuals with BD experience another co-occurring psychiatric illness during their lifetime.⁶ Of all psychiatric conditions, BD is the most likely to co-occur with alcohol or drug abuse disorders.⁷

Treatment of BD generally begins with the goal of bringing a patient with mania or depression to symptomatic recovery and stable mood. Once the individual is stable, the goal progresses to reducing subthreshold symptoms and preventing relapse into full-blown episodes of mania and depression. Drug treatments have several purposes. Some drugs aim to reduce symptoms associated with acute manic or mixed mania/depression episodes, some aim to reduce acute depression symptoms, and others aim to reduce acute symptoms, maintain relatively symptom-free periods, and prevent relapsing to acute episodes. Given the chronic, relapsing/remitting course of bipolar disorder and the need for maintenance treatment in many patients, drugs begun for an acute mood episode (including mania) are often carried forward into maintenance therapy.

Nondrug psychosocial therapeutic approaches range from psychoeducational, cognitive behavioral, and family-focused therapies, to interpersonal social rhythm therapy, and are provided both in individual and group therapy modalities. Most psychosocial therapeutic approaches focus the treatment for individuals currently in the remission state of bipolar illness and often specifically exclude individuals currently in acute manic episodes. Other nondrug treatment forms range widely from electroconvulsive therapy to treatments for circadian rhythms (such as light boxes), to acupuncture, to repetitive transcranial magnetic stimulation.

This review provides a comprehensive up-to-date synthesis of the evidence on the effects of a broad range of BD interventions (drug and nondrug). We excluded botanicals and nutritional supplements. These are part of a broader class of remedies patients may take on their own for symptom relief.

The review addresses the benefits and harms of pharmacologic and nonpharmacologic treatment interventions for adults with any type of BD. Two additional questions regarding treatments to reduce metabolic change side effects of drug treatments, and how effects differ by patient characteristics, such as co-occurring substance abuse, were not answerable with the available literature. Reported results focus on Key Questions 1 and 2.

Methods

The review used methods following Agency for Healthcare Research and Quality methods guidance. The protocol was posted June 23, 2014 at <https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1926>.

Eligible studies included randomized controlled trials and prospective cohorts with comparator arms enrolling adults with BD of any type with followup of 3 weeks for acute mania, 3 months for depression, and 6 months for maintenance treatments. We excluded studies with greater than 50 percent attrition (with the exception of maintenance studies with time-to-relapse and withdrawal outcomes) because of potential systematic differences between patients who do not complete the study and those who do. That is, attrition may not be random and/or is likely due to BD or treatment-relevant factors.

We used published minimally important differences (MIDs) to interpret findings for the Young Mania Rating Scale (YMRS) (MID=6) and the Clinical Global Impressions (CGI) scale (MID=1).⁸ If a change in an outcome is at least equal to the MID, the interpretation that all participants benefitted from the intervention is clear. However, because the actual benefit each participant experiences lies somewhere along a distribution of benefits recorded for all the participants, changes less than an MID may also suggest that at least some of the participants benefitted from the intervention.⁹ We therefore followed a rule for interpretation that if an estimate of outcome is greater than 50 percent of the MID, it is possible that a reasonable proportion of participants received the benefit. Conversely, if the estimate is less than 50 percent of the MID, it is much less likely that an appreciable proportion received benefit from the treatment.

Results

We identified 6,116 unique publications through May 2017, of which 188 were eligible for our review; 123 publications of drug interventions, 65 publications for nondrug interventions. The publications comprised 67 unique drug studies for acute mania, seven drug studies for depression, 36 drug studies for maintenance, 48 for psychosocial therapies, and one study on repetitive transcranial magnetic stimulation. All acute mania treatment studies enrolled adults with BD-I; only two also explicitly included BD-II, and only one BD not otherwise specified (NOS). All depression treatment studies included adults with BD-II, while two also included BD-I. Fifteen of the 36 maintenance drug studies (42%) included BD participants other than BD-I, but only five studies also included BD NOS. The nondrug studies were more inclusive in their included BD populations.

We found no high- or moderate-strength evidence for any intervention to effectively treat any type of BD compared to placebo or an active comparator. We found scattered evidence for some drug interventions that were assessed as low-strength for adults with BD-I, but none for adults with BD-II or BD-NOS. However, most manic symptom improvements were of modest clinical significance, with values that were less than the MID but still large enough that a reasonable proportion of participants likely received a benefit. Very few findings for psychosocial interventions were assessed as low strength.

Table A provides a summary of low-strength evidence findings from the results chapters detailing intervention results. A full reporting of results and evidence tables can be found in the full report.

Table A. Summary of low-strength* evidence findings by intervention class

Category	Intervention	# Studies/ Design (n Analyzed) Timing	Findings (Low Strength)
Antipsychotics for acute mania	Asenapine vs. placebo	3 RCT ¹⁰⁻¹² (n=936) 3 weeks	Response/Remission Rates: No difference YMRS: Favors Asenapine, MD 4.37 (95% CI 1.27, 7.47; MID 6) CGI-BP-S: Favors Asenapine, MD 0.5 (95% CI 0.29, 0.71; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference
	Cariprazine vs. placebo	3 RCT ¹³⁻¹⁵ (n=1,047) 3 weeks	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT=5.6 Remission Rate: Favors Cariprazine, OR 1.95 (95% CI 1.45, 2.63); NNT= 7 YMRS: Favors Cariprazine, MD 5.38 (95% CI 1.84, 8.92; MID 6) CGI-BP-S: Favors Cariprazine, MD 0.54 (95% CI 0.35, 0.73; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference
	Olanzapine vs. placebo	5 RCT ^{11, 16-19} (n=1199) 3 weeks	Response Rate: Favors Olanzapine, OR 1.99 (95% CI 1.29, 3.08); NNT=6 Remission Rate: Favors Olanzapine, OR 1.75 (95% CI 1.19, 2.58); NNT=7.5 YMRS: Favors Olanzapine, MD 4.9 (95% CI 2.34, 7.45; MID 6) Withdrawal (Lack of Efficacy, Overall): Favors Olanzapine, MD 0.42 (95% CI 0.29, 0.61)
		3 RCT ^{16, 18, 19} (n=611) 3 weeks	CGI-BP-S: No difference
	Quetiapine vs. placebo	4 RCT ²⁰⁻²³ (n=1,007) 3 weeks	Response Rate: Favors Quetiapine, OR 2.07 (95% CI 1.39, 3.09); NNT=6.2 Withdrawal (Lack of Efficacy): Favors Quetiapine, MD 0.38 (95% CI 0.23, 0.63)
		5 RCT ²⁰⁻²⁴ (n=699) 3 weeks	YMRS: Favors Quetiapine, MD 4.92 (95% CI 0.31, 9.53; MID 6)
		5 RCT ²⁰⁻²⁴ (n=806) 3 weeks	CGI-BP-S: Favors Quetiapine, MD 0.54 (95% CI 0.35, 0.74; MID 1)
	Risperidone vs. placebo	2 RCT ^{25, 26} (n=584) 3 weeks	Response Rate, YMRS, and CGI: Favors Risperidone (not pooled)
	Ziprasidone vs. placebo	2 RCT ^{27, 28} (n=402) 3 weeks	Response Rate, YMRS, and CGI: Favors Ziprasidone (not pooled)
	Olanzapine vs. Divalproex/ Valproate	2 RCTs ^{18, 29} (n=635) 3 weeks	Response and Remission: No difference
		3 RCTs ^{18, 29, 30} (n=750) 3 weeks	YMRS: No difference
		3 RCTs ^{18, 29, 30} (n=578) 3 weeks	CGI: No difference
		4 RCTs ^{18, 29-31} (n=867) 3 weeks	Withdrawals: No difference

Category	Intervention	# Studies/ Design (n Analyzed) Timing	Findings (Low Strength)
Mood stabilizers treatments for acute mania	Lithium vs. placebo	1 RCT ²¹ + 1 IPD ³² (n=325) 3 weeks	Remission and Response Rates: Favors Lithium (not pooled)
		3 RCTs ^{21, 32} (n=325) 3 weeks	YMRS: Favors Lithium, MD 5.81 (95% CI 2.21, 9.4; MID 6) Withdrawal (Overall): No difference
		1 IPD ³² (n=450) 3 weeks	Withdrawal (Lack of Efficacy, AE): No difference
Other drug treatments for mania	Paliperidone vs. placebo	2 RCT ^{20, 33} (n=763) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): Favors Paliperidone (possible dose response: No difference at 3 and 6 mg, benefit at 12 mg or median dosage of 9 mg) Withdrawal (AE): No difference
	Topiramate vs. placebo	1 IPD ³² (n=876) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): No difference Withdrawals (Overall): Favors Placebo, 37.2% vs. 26.8%, p=0.005 Withdrawals (AE): Favors Placebo, 6.04% vs. 2.84%, p=0.049
	Topiramate vs. lithium	1 IPD ³² (n=453) 3 weeks	YMRS: Favors Lithium, MD 6.14 (95% CI 3.94, 8.34; MID 6)
		1 IPD ³² (n=453) 3 weeks	Withdrawal (Overall, AE): No difference
		1 IPD ³² (n=453) 3 weeks	Withdrawal (AE): Favors Topiramate, 2.65% vs. 7.49%, p=0.019
	Allopurinol + lithium vs. placebo + lithium	4 RCT ³⁴⁻³⁷ (n=355) 4 weeks	YMRS, CGI, Withdrawal (Overall): No difference
Single drug treatment for maintenance	Lithium vs. placebo	6 RCT ³⁸⁻⁴³ (n=1579) 1 to 2 years	Time to overall relapse: Favors Lithium
Psychosocial interventions	CBT vs. Active Comparators**	5 RCTs ⁴⁴⁻⁴⁹ (n=461) 6 to 12 months	Depression and Mania symptoms: No difference between groups across range of time periods.
	Systematic or Collaborative Care vs. Inactive Comparators†	2 RCTs ^{50, 51} (n=599) 7 to 12 months	Relapse Rate: No difference between groups across different time periods.

*All findings are low-strength evidence based generally on moderate study limitations and imprecision. ** Active comparators are comparators such as a different psychosocial therapy or peer support. †Inactive comparators are comparators such as usual care, no intervention.

AE=adverse events; CBT=cognitive behavioral therapy; CGI =Clinical global impression; CGI-BP-S=Clinical global impression scale for bipolar severity; CI=confidence interval; IPD=individual patient data; MD=mean difference; MID=minimal important difference; NNT=number needed to treat; OR=odds ratio; RCT=randomized controlled trial; YMRS=Young mania rating scale

Asenapine, cariprazine, quetiapine, and olanzapine improved acute mania symptoms compared to placebo (low-strength evidence). However, improvements were of modest clinical significance, with values that were less than the MID, but still large enough that a reasonable proportion of participants likely received a benefit. Unpooled evidence indicated an overall beneficial effect of risperidone and ziprasidone on acute mania symptoms compared to placebo

(low-strength evidence). Lithium improved acute mania in the short-term and prolonged time to relapse in the long-term compared to placebo (low-strength evidence). No difference was found between olanzapine and divalproex/valproate for acute mania (low-strength evidence). For drugs not approved for BD, paliperidone also improved acute mania compared to placebo (low-strength evidence), while topiramate and allopurinol showed no benefit (low-strength evidence). Further, lithium improved acute mania better than topiramate (low-strength evidence), although withdrawals for adverse events were lower for topiramate. Only lithium reached a minimally important difference for acute mania and maintenance treatment. All other drug comparisons to placebo or active controls for acute mania, depression, and maintenance had insufficient evidence.

Adverse events for drugs were variously reported and generally not with sufficient detail to allow pooling when multiple studies were available. When reported, all drug comparisons generally showed no differences between groups in serious adverse events. Participants using atypical antipsychotics as a single drug, except quetiapine, experienced more extrapyramidal symptoms compared to placebo. Participants using haloperidol experienced more extrapyramidal symptoms compared to other antipsychotics. Participants using olanzapine reported more clinically significant weight gain. Participants using carbamazepine reported more severe rash and number of adverse events compared to placebo.

For psychosocial interventions, cognitive behavioral training (CBT) was no better for depression or mania symptoms than psychoeducation or other active psychosocial comparators (low-strength evidence). Systematic/collaborative care had no effect on relapse compared to inactive comparators (low-strength evidence).

Table B provides a list of interventions and comparators with evidence that was insufficient to draw conclusions.

Table B. Interventions/comparators with insufficient strength of evidence

Category	Drug	Comparator
Antipsychotics for mania	Aripiprazole	Placebo
	Aripiprazole	Haloperidol
	Aripiprazole plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Aripiprazole plus Mood Stabilizers	Haloperidol plus Mood Stabilizer
	Asenapine	Olanzapine
	Asenapine plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Olanzapine (for withdrawal for adverse events only)	Placebo
	Olanzapine	Haloperidol or Lithium or Risperidone
	Olanzapine plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Olanzapine plus Mood Stabilizers	Mood Stabilizer alone (no placebo)
	Quetiapine	Haloperidol or Lithium
	Quetiapine plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Risperidone	Haloperidol or Lithium
	Risperidone plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Ziprasidone plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Ziprasidone plus Mood Stabilizer	Chlorpromazine plus Mood Stabilizer
Mood Stabilizers for mania	Haloperidol	Placebo
	Carbamazepine	Placebo
	Divalproex/Valproate	Placebo
	Valproate	No Placebo
	Lithium (for CGI only)	Placebo
	Carbamazepine	Lithium or Valproate
	Carbamazepine	Valproate
	Lamotrigine	Lithium

Category	Drug	Comparator
Other Drugs for mania	Lithium	Haloperidol or Divalproex
	Paliperidone (for Remission, Response, CGI Withdrawal (Overall))	Placebo
	Allopurinol plus Lithium (for Response and Remission)	Lithium alone (placebo)
	Allopurinol plus Lithium	Dipyridamole plus Lithium
	Celecoxib	Placebo
	Dipyridamole plus Lithium	Lithium alone (placebo)
	Donepezil plus Lithium	Lithium alone (placebo)
	Endoxifen	Divalproex
	Gabapentin plus Lithium	Lithium alone (placebo)
	Oxcarbazepine	Divalproex
	Paliperidone Extended Release	Olanzapine or Quetiapine
	Paliperidone plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Tamoxifen	Placebo
	Topiramate plus Risperidone	Divalproex plus Risperidone
	Topiramate and Mood Stabilizer	Mood Stabilizer alone (placebo)
Drugs for depression	Memantine plus Valproate	Valproate alone (placebo)
	Lamotrigine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Antidepressives (paroxetine, bupropion, or both)	Placebo
	Sertraline	Lithium
	Venlafaxine	Lithium
	Lithium and OPT	OPT alone
Drugs for maintenance	Long-acting Injectable Aripiprazole	Placebo
	Aripiprazole	Placebo
	Aripiprazole plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Carbamazepine	Lithium
	Divalproex	Placebo
	Divalproex plus Lithium	Lithium alone (placebo)
	Fluoxetine	Placebo
	Fluoxetine	Lithium
	Gabapentin plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Lamotrigine	Placebo
	Lamotrigine for pregnant women	Discontinue Mood Stabilizers
	Lamotrigine	Lithium
	Lithium	Placebo
	Lithium	Divalproex/Valproate
	Olanzapine	Placebo
	Olanzapine	Divalproex
	Olanzapine	Lithium
	Olanzapine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Oxcarbazepine plus Lithium	Lithium alone (placebo)
	Paliperidone	Placebo
	Paliperidone	Olanzapine
	Perphenazine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Quetiapine	Placebo
	Quetiapine	Lithium
	Quetiapine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Quetiapine and Personalize Treatment	Lithium and Personalized Treatment
	Risperidone	Placebo
	Risperidone	Olanzapine
	Risperidone Long Acting Injectable and Treatment as Usual	Placebo and Treatment as Usual

Category	Drug	Comparator
	Valproic Acid plus Aripiprazole	Lithium plus Aripiprazole
	Venlafaxine	Lithium
	Ziprasidone and Mood Stabilizers	Mood Stabilizers alone (placebo)
Psychosocial Interventions	Psychoeducation	Inactive* Comparators
	Psychoeducation	Active** Comparators
	CBT	Inactive Comparators
	CBT (for Relapse, Global Function, Other Measures of Function)	Active Comparators
	Systematic or Collaborative Care (for Depression, Mania, Global Function, Other Measures of Function)	Inactive Comparators
	Family or Partner Interventions	Inactive Comparators
	Family or Partner Interventions	Active Comparators
	IPSRT	Inactive Comparators
	IPSRT	Active Comparators
	Combination Interventions	Inactive Comparators
	Combination Interventions	Active Comparators
	Other Psychosocial Interventions	Inactive Comparators
Somatic	Repetitive transcranial magnetic stimulation	Sham stimulation

*Inactive comparators include usual care or no intervention. **Active comparators include a different psychosocial therapy, peer support, or similar.

CBT=cognitive behavioral therapy; CGI=Clinical Global Impression; IPSRT= Interpersonal and Social Rhythm Therapy; OPT=Optimal Personalized Treatment

Discussion

This review found only low-strength evidence for treatments for adults with BD. All Food and Drug Administration-approved antipsychotics, except aripiprazole, improved mania symptoms when compared to placebo for acute mania in adults with BD-I. However, none of the drugs reached MID. Participants using atypical antipsychotics, except quetiapine, reported more extrapyramidal symptoms compared to placebo, and those using olanzapine reported more clinically significant weight gain. Lithium showed short-term benefit for acute mania and longer time to relapse to any mood episode in adults with BD-I versus placebo. Of all acute mania treatments, lithium treatment was closest to reaching a clinically meaningful difference for all the participants as measured by the MID. Evidence was generally insufficient for benefits from nondrug interventions for adults with BD. Low-strength evidence showed no effect for the effectiveness of CBT on bipolar symptoms and the efficacy of systematic/collaborative care on preventing relapse.

Our findings are consistent with other systematic reviews of treatments for bipolar; however, because we excluded studies with greater than 50 percent attrition rates, our findings are more conservative than those of other reviews. Similar to Cochrane reviews, we also found benefit for olanzapine and risperidone compared with placebo for mania, and benefit for lithium compared with placebo for maintenance.⁵²⁻⁵⁴ Cochrane reviews have reported benefit for several additional antipsychotics compared with placebo – aripiprazole, haloperidol as single drug and added to mood stabilizers, and olanzapine or risperidone plus mood stabilizers – whereas we found evidence was insufficient.^{52, 55-58} However, authors of these reviews consistently noted that issues with attrition and medication adherence may have impacted their results. Insufficient evidence for psychosocial interventions was consistent across all reviews.^{59, 60}

Applicability of the review findings is challenging. The trials for drug treatments used restrictive exclusion criteria, making it difficult to determine whether the findings extend to

adults with BD-II, or BD-I with a first manic episode, current comorbid substance use, pregnant or nursing women, or older adults (i.e., age 65 and over).

Conversely, most psychosocial trials provided too little information on the participant characteristics, limiting the ability to infer from the results. Mixtures of participants may mask patterns of effectiveness. With the current information, we cannot determine if or to what extent this contributed to the few findings of nonsignificance between groups.

Applicability is further challenged by high attrition rates. Trials with 20 to 50 percent attrition, such as were used in this review, at best provide an estimate of the efficacy or comparative effectiveness of a treatment for participants who comply with, tolerate, and, in some minimal sense, benefit from the treatment. However, at extremely high levels of attrition, even this interpretation is of limited value to clinicians.⁶¹ Likewise, the maintenance trials are most applicable to people with BD-I who respond to initial treatment.

Applicability is also hindered by lack of information about diagnostic accuracy. The accuracy of a diagnosis of BD, or study eligibility, depends on the interviews or screening tools, the criteria used to diagnose BD, and who performs the diagnostic assessment. Additional information and rigor in diagnostic assessment would generate a greater sense of confidence about who the study participants represent and, therefore, the populations to which the study results apply. Uncertainty and debate surround the question of whether the underlying mechanisms support the bipolar types as qualitatively and categorically different or as lying on a continuum of the same psychopathological dimensions. Meanwhile, the importance of diagnostic accuracy is further underscored by the great difficulty in accurately diagnosing the comorbid mental health conditions that were commonly treated as exclusion criteria in the studies we reviewed.

Limitations

Several inclusion criteria may have created limitations to the review findings. We only included studies if the populations were exclusively adults with BD, or if the bipolar subpopulation results were reported separately. Psychosocial treatments specific to depression or mania that combined participants with bipolar and nonbipolar diagnoses in analyses may have been missed and therefore not included in this review.

In addition to clearly reported outcomes for BD populations, we also required studies to be at least prospective cohort studies with comparator. This combination of inclusion criteria led to a number of observational studies being excluded, including those that looked at broad classes of drugs, or individual drugs across broad populations. Thus, harms information was essentially limited to RCTs or extensions of RCTs.

We also looked at minimum followup periods of 3 weeks for acute mania studies, 3 months for depression studies, and 6 months for maintenance studies. This criteria led to many studies, especially for depression treatment and other somatic treatments such as electroconvulsive therapy, being excluded for followup times that were too short. However, given the chronic nature of bipolar disorders, the clinical relevance of short followup studies is questionable. Moreover, evidence that a treatment reduces bipolar episode relapse rates likely requires followup longer than 12 months, because some individuals with bipolar disorder only experience episodes once or twice per year.

Research Needs

Future studies of BD treatments need to consider innovative ways to increase study completion rates (e.g., use of technology for followup assessments and study reminders; “smart” bottles for assessing study drug adherence; multiple secondary contacts for participants and all-inclusive contact information from cell phones, email, to social media; flexible scheduling outside of business hours, availability at the last minute notice). More longitudinal data analysis techniques for intermittent followup would help, but that requires more effort to create data repositories that allow individual patient-level data pooling of these longitudinal studies. Such repositories could also help broaden inclusion criteria and allow for further subpopulation analyses. Future research should also enroll people with different patient characteristics and initial episodes and maintenance stages to fully understand the spectrum of responses. Attention should be given to addressing all states of the illness throughout the treatment stream.

Conclusion

We found no high or moderate-strength evidence for any intervention to effectively treat any phase of any type of BD compared to placebo or an active comparator. Low-strength evidence showed improved mania symptoms for all Food and Drug Administration-approved antipsychotics, except aripiprazole, when compared to placebo for adults with BD-I. Low-strength evidence also showed benefit from lithium in the short-term for acute mania and longer time to relapse in the long-term versus placebo in adults with BD-I. Evidence was insufficient for most nondrug interventions. Aside from low-strength evidence showing CBT and systematic/collaborative care having no benefit for a few outcomes, evidence was insufficient for psychosocial interventions. We were unable to address questions on subpopulations or treatments to reduce the metabolic-related side effects of first-line drug treatments. Future studies of treatments for BD will require innovative ways to increase study completion rates.

References

1. Ferrari AJ, Stockings E, Khoo JP, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study 2013. *Bipolar Disord.* 2016 01 Aug;18(5):440-50. doi: <http://dx.doi.org/10.1111/bdi.12423>. PMID: 611908711.
2. Gum A, King-Kallimanis B, Kohn R. Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. *Am J Geriatr Psychiatry.* 2009;17:769-81.
3. Samame C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. *Acta Psychiatr Scand.* 2012;125(4):266-80.
4. Sole B, Martinez-Aran A, Torrent C, et al. Are bipolar II patients cognitively impaired? A systematic review. *Psychol Med.* 2011;41(9):1791-803.
5. Schaffer A, Isometsa ET, Tondo L, et al. Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. *Aust N Z J Psychiatry.* 49(9):785-802. PMID: 26185269.

6. Merikangas K, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007 May;64(5):543-52. PMID: 17485606.
7. Brady KT, Sonne S. The relationship between substance abuse and bipolar disorder. *J Clin Psychiatry*. 1995;56(Suppl 3):19-24. PMID: 7883738
8. Lukasiewicz M, Gerard S, Besnard A, et al. Young mania rating scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort. *Int. J. Methods Psychiatr. Res*. 2013;22(1):46-58. doi: 10.1002/mpr.1379. PMID: 23526724.
9. Johnston BC, Patrick DL, Thorlund K, et al. Patient-reported outcomes in meta-analyses – Part 2: methods for improving interpretability for decision-makers. *Health and Quality of Life Outcome*. 2013;11(211)doi: doi:10.1186/1477-7525-11-211. PMID: 24359184.
10. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2010 Apr;122(1-2):27-38. doi: <http://dx.doi.org/10.1016/j.jad.2009.12.028>. PMID: 20096936.
11. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states.[Erratum appears in *Bipolar Disord*. 2010 May;12(3):350]. *Bipolar Disord*. 2009 Nov;11(7):673-86. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00748.x>. PMID: 19839993.
12. Landbloom RL, Mackle M, Wu X, et al. Asenapine: Efficacy and safety of 5 and 10mg bid in a 3-week, randomized, double-blind, placebo-controlled trial in adults with a manic or mixed episode associated with bipolar I disorder. *J Affect Disord*. 2016 Jan 15;190:103-10. doi: <http://dx.doi.org/10.1016/j.jad.2015.06.059>. PMID: 26496015.
13. Calabrese JR, Keck PE, Jr., Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015 Mar;76(3):284-92. doi: <http://dx.doi.org/10.4088/JCP.14m09081>. PMID: 25562205.
14. Durgam S, Starace A, Li D, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015 Feb;17(1):63-75. doi: <http://dx.doi.org/10.1111/bdi.12238>. PMID: 25056368 (pubmed) 2014-30788-001(Psychinfo).
15. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord*. 2015 Mar 15;174:296-302. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.018>. PMID: 25532076.
16. Katagiri H, Takita Y, Tohen M, et al. Efficacy and safety of olanzapine in the treatment of Japanese patients with bipolar I disorder in a current manic or mixed episode: a randomized, double-blind, placebo- and haloperidol-controlled study. *J Affect Disord*. 2012 Feb;136(3):476-84. doi: <http://dx.doi.org/10.1016/j.jad.2011.10.045>. PMID: 22134043.
17. McIntyre RS. Aripiprazole for the maintenance treatment of bipolar I disorder: A review. *Clin Ther*. 2010;32 Suppl 1:S32-8. doi: <http://dx.doi.org/10.1016/j.clinthera.2010.01.022>. PMID: 20152551.
18. Tohen M, Vieta E, Goodwin GM, et al. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *J Clin Psychiatry*. 2008 Nov;69(11):1776-89. PMID: 19014751.
19. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group.[Erratum appears in *Arch Gen Psychiatry* 2002 Jan;59(1):91]. *Arch Gen Psychiatry*. 2000 Sep;57(9):841-9. PMID: 10986547.
20. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord*. 2010 May;12(3):230-43. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00815.x>. PMID: 20565430.
21. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry*. 2005 Jan;66(1):111-21. PMID: 15669897.

22. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2005 Oct;15(5):573-85. PMID: 16139175.
23. Cutler AJ, Datto C, Nordenhem A, et al. Extended-release quetiapine as monotherapy for the treatment of adults with acute mania: a randomized, double-blind, 3-week trial. *Clin Ther*. 2011 Nov;33(11):1643-58. doi: <http://dx.doi.org/10.1016/j.clinthera.2011.10.002>. PMID: 22054797.
24. McElroy SL, Martens BE, Winstanley EL, et al. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *J Affect Disord*. 2010 Jul;124(1-2):157-63. doi: <http://dx.doi.org/10.1016/j.jad.2009.11.014>. PMID: 19963274.
25. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania. *Br J Psychiatry*. 2005 2005;187(3):229-34. doi: <http://dx.doi.org/10.1192/bjp.187.3.229>. PMID: 16135859.
26. Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol*. 2005 Jan;15(1):75-84. PMID: 15572276.
27. Potkin SG, Keck PE, Jr., Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005 Aug;25(4):301-10. PMID: 16012271.
28. Keck PE, Jr., Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003 Apr;160(4):741-8. PMID: 12668364.
29. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania.[Erratum appears in *Am J Psychiatry*. 2005 Feb;7(1):102]. *Am J of Psychiatry*. 2002 Jun;159(6):1011-7. PMID: 12042191.
30. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clinical Psychiatry*. 2002 Dec;63(12):1148-55. PMID: 12523875.
31. Xu L, Lu Y, Yang Y, et al. Olanzapine-valproate combination versus olanzapine or valproate monotherapy in the treatment of bipolar imania: A randomized controlled study in a chinese population group. *Neuropsychiatric Disease and Treatment*. 2015 25 May;11:1265-71. doi: <http://dx.doi.org/10.2147/NDT.S81146>. PMID: 26060401 (pubmed) 2015078440 (embase).
32. Kushner SF, Khan A, Lane R, et al. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord*. 2006 Feb;8(1):15-27. PMID: 16411977.
33. Berwaerts J, Xu H, Nuamah I, et al. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *J Affect Disord*. 2012 Jan;136(1-2):e51-60. doi: <http://dx.doi.org/10.1016/j.jad.2010.06.030>. PMID: 20624657.
34. Jahangard L, Soroush S, Haghighi M, et al. In a double-blind, randomized and placebo-controlled trial, adjuvant allopurinol improved symptoms of mania in in-patients suffering from bipolar disorder. *Eur Neuropsychopharmacol*. Jun. 2014 2, 2014(Pagination)doi: <http://dx.doi.org/10.1016/j.euroneuro.2014.05.013>. PMID: 24953766.
35. Weiser M, Burshtein S, Gershon AA, et al. Allopurinol for mania: A randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. *Bipolar Disord*. 2014 2014;16(4):441-7. doi: <http://dx.doi.org/10.1111/bdi.12202>. PMID: 24712840.
36. Fan A, Berg A, Bresee C, et al. Allopurinol augmentation in the outpatient treatment of bipolar mania: a pilot study. *Bipolar Disord*. 2012 Mar;14(2):206-10. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.01001.x>. PMID: 22420596.

37. Machado-Vieira R, Soares JC, Lara DR, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. *J Clin Psychiatry*. 2008 Aug;69(8):1237-45. PMID: 18681754.
38. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.[Erratum appears in *Arch Gen Psychiatry*. 2004 Jul;61(7):680]. *Arch Gen Psychiatry*. 2003 Apr;60(4):392-400. PMID: 12695317.
39. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003 Sep;64(9):1013-24. PMID: 14628976.
40. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. *Am J Psychiatry*. 2010 Jul;167(7):792-800. doi: <http://dx.doi.org/10.1176/appi.ajp.2009.09020284>. PMID: 20360317.
41. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry*. 2000 May;57(5):481-9. PMID: 10807488.
42. Prien RF, Point P, Caffey EM, et al. Prophylactic efficacy of lithium carbonate in manic-depressive illness: Report of the veterans administration and national institute of mental health collaborative study group. *Arch Gen Psychiatry*. 1973;28(3):337-41. doi: 10.1001/archpsyc.1973.01750330035006. PMID: 4569674.
43. Weisler RH, Nolen WA, Neijber A, et al. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *J Clin Psychiatry*. 2011 Nov;72(11):1452-64. doi: <http://dx.doi.org/10.4088/JCP.11m06878>. PMID: 22054050.
44. Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. *Br J Psychiatry*. 2010 May;196(5):383-8. doi: <http://dx.doi.org/10.1192/bjp.bp.108.058263>. PMID: 20435965.
45. Lam DH, Hayward P, Watkins ER, et al. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. *American Journal of Psychiatry*. 2005 Feb;162(2):324-9. PMID: 15677598.
46. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Archives of General Psychiatry*. 2003 Feb;60(2):145-52. PMID: 12578431.
47. Jones SH, Smith G, Mulligan LD, et al. Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial.[Erratum appears in *Br J Psychiatry*. 2015 Feb;206(2):169]. *Br J Psychiatry*. 2015 Jan;206(1):58-66. doi: <http://dx.doi.org/10.1192/bjp.bp.113.141259>. PMID: 25213157.
48. Perich T, Manicavasagar V, Mitchell PB, et al. A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. *Acta Psychiatrica Scandinavica*. 2013 May;127(5):333-43. doi: <http://dx.doi.org/10.1111/acps.12033>. PMID: 23216045.
49. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry*. 2006 Apr;188:313-20. PMID: 16582056.
50. Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br J Psychiatry*. 2013 Mar;202(3):212-9. doi: <http://dx.doi.org/10.1192/bjp.bp.112.113548>. PMID: 23349295.
51. Simon GE, Ludman EJ, Unutzer J, et al. Randomized trial of a population-based care program for people with bipolar disorder. *Psychol Med*. 2005 Jan;35(1):13-24. PMID: 15842025.
52. Rendell Jennifer M, Gijsman Harm J, Keck Paul K, et al. Olanzapine alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2003.

53. Rendell Jennifer M, Gijsman Harm J, Bauer Mark S, et al. Risperidone alone or in combination for acute mania. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2006.
54. Burgess Sally SA, Geddes J, Hawton Keith KE, et al. Lithium for maintenance treatment of mood disorders. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2001.
55. Rendell Jennifer M, Geddes J. Risperidone in long-term treatment for bipolar disorder. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2006.
56. Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2013.
57. Cipriani A, Rendell Jennifer M, Geddes J. Olanzapine in long-term treatment for bipolar disorder. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2009.
58. Cipriani A, Rendell Jennifer M, Geddes J. Haloperidol alone or in combination for acute mania. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2006.
59. Swartz H, Swanson J. Psychotherapy for bipolar disorder in adults: a review of the evidence. Focus (Am Psychiatr Publ). 2014 Summer;12(3):251-66. doi: 10.1176/appi.focus.12.3.251. PMID: 26279641.
60. Reilly S, Planner C, Gask L, et al. Collaborative care approaches for people with severe mental illness. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2013.
61. Council NR. The prevention and treatment of missing data in clinical trials: National Academies Press; 2011.

Chapter 1. Introduction

Background

Bipolar disorder, also known as manic-depressive illness, is a serious mental illness that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. The Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5)¹ defines mania and hypomania as bipolar episodes characterized by elation, or irritability, and increased energy, plus at least three additional symptoms (four if the predominant mood is irritability): increased pursuit of various goal-directed activities without concern for potential negative consequences (e.g., impulsive shopping, risky business undertakings, unsafe sexual behaviors); increased activity level or psychomotor restlessness; pressured speech or greater talkativeness; a subjective feeling that one's thoughts are racing or jumping from topic to topic; increased distractibility by stimuli in the environment; and exaggerated self-confidence, at times to the point of grandiose delusions (e.g., believing one has special abilities or powers). Bipolar depressive episodes are characterized by depressed mood or anhedonia (i.e., a lack of interest in pleasurable activities) and at least four additional symptoms: decreased energy; psychomotor slowing or psychomotor restlessness; changes in appetite and weight; sleep disturbance (from insomnia to hypersomnia); difficulty concentrating and/or inability to make everyday decisions; feelings of worthlessness and/or excessive guilt; and suicidal ideation and attempts.

Manic and depressive episodes can vary in symptom duration and severity as well as subsequent effects on everyday functioning; therefore, the DSM-5 recognizes a spectrum of bipolar diagnoses that differ in duration of bipolar episodes/periods and impairment: bipolar I, bipolar II, other specified bipolar and related disorder, and unspecified bipolar and related disorder. The latter two diagnoses were captured under the bipolar disorder not otherwise specified diagnosis in prior versions of the DSM (DSM-IV-TR; 2000) and in current research literature.

According to the DSM-5, bipolar I disorder is mainly defined by the presence of manic episodes that last at least seven days, or by manic symptoms severe enough to necessitate immediate hospital care. Mania symptoms must reflect a major change from the person's normal behavior and cause grave impairment. Usually, a person with bipolar I disorder also has depressive episodes, typically lasting at least two weeks, which significantly impair daily functioning or distress. Still, presence of depressive episodes is not necessary for bipolar I disorder diagnosis. Prior DSM versions and empirical literature also allowed for bipolar I disorder diagnosis based on the presence of mixed episodes, i.e., periods of one week or longer characterized by both manic and depressive symptoms. The DSM-5 omits language specifying that individuals meet the full criteria for both mania and a major depressive episode in favor of a new specifier, "with mixed features." Mixed features is applicable to episodes of mania or hypomania when depressive features are present, and to episodes of depression when features of mania/hypomania are present. The associated symptom of psychosis can also shift the episode type from hypomania to mania.

Bipolar II disorder is defined by a pattern of depressive episodes alternating with hypomanic episodes, but no full-blown manic episodes. Diagnostic criteria specify that hypomanic episodes, lasting at least four days, must cause a change in functioning observable by others, but this change could be positive (i.e., more productive, social) and not impairing. Cyclothymic disorder is defined by many periods of hypomanic and depressive symptoms, but these symptoms do not reach the level of clinical hypomanic or depressive episodes.

Bipolar disorder definitions for forms not reaching bipolar I and bipolar II disorder criteria have recently been reorganized and redefined. DSM-5 presented four different case scenarios for “other specified bipolar disorder,” including a) history of major depressive episodes and hypomanic periods that meet episode criteria except for duration (i.e., last less than four days); b) history of major depressive episodes and hypomanic periods of sufficient duration but insufficient number of symptoms to meet episode criteria; c) history of hypomanic episodes without major depressive episodes; and d) criteria for cyclothymia met for less than two years. Other cases of failing to meet bipolar I or II disorder diagnoses would fit the unspecified bipolar disorder category. DSM-5 has also further specified that cyclothymic disorder cannot be comorbid/or jointly assigned along with bipolar I or II disorder (e.g., if an individual develops episodes, the diagnosis would change to the type that best reflects new symptoms).

Structured psychiatric interviews, such as the Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I), or the MINI International Neuropsychiatric Interview (MINI), are widely used in research settings and provide reliable diagnoses when conducted by trained interviewers.² The structured interviews help differentiate bipolar disorders from other common diagnoses, such as borderline personality disorder, as well as between various bipolar disorder definitions. However, such structured interviews are not as common in regular clinical settings, where screening questionnaires and clinical interviews are more often used to identify new bipolar diagnoses or changes in patient symptoms.

Prevalence studies estimate about 1 percent of the population for bipolar I disorder, another 1 percent for bipolar II disorder, and up to 5 percent for the full spectrum of bipolar disorder diagnoses, with relatively similar prevalence in men and women, and across cultural and ethnic groups.^{3, 4} Recurrent episodes of mania and depression can cause serious impairments in functioning, such as erratic work performance, increased divorce rates, and psychosocial morbidity.^{5, 6} People with bipolar disorder account for between 3 and 14 percent of all suicides.⁷ About 25 percent of bipolar disorder patients will attempt suicide.⁷ The disease burden is heavy, with lifelong treatment requirements.

Further adding to the individual illness burden, 92 percent of individuals with bipolar disorder experience a co-occurring psychiatric illness during their lifetime.⁸ Substance abuse is a common comorbid condition; of all psychiatric conditions, bipolar disorder is the most likely to co-occur with alcohol or drug abuse.⁹ Thus, it is important to identify not just effective treatments for bipolar disorder alone, but effective treatments for individuals experiencing both bipolar symptoms and co-occurring substance abuse and other psychiatric illnesses.

Increasingly, empirical evidence supports disruption of specific neural circuits as a factor in bipolar disorders. However, the exact mechanisms that lead to onset of bipolar disorders are still not fully understood. This further complicates a search for effective treatments.

Treatment Strategies

Treatment generally begins with the goal of bringing a patient with mania, or disabling hypomania, or depression to symptomatic recovery and stable mood. Upon stabilization, maintenance treatment (both drug and nondrug options) aims to maintain euthymia (a nondepressed, reasonably positive mood), reduce any subthreshold symptoms (milder but still clinically significant symptoms), and prevent or delay relapse into full-blown episodes of mania and depression. Questions remain as to whether treatment effects differ by patient characteristics which may impact condition severity or treatment response.

Drug treatments are used to reduce acute symptoms, maintain relatively symptom-free periods, and reduce risk of relapsing to acute episodes. Drug treatments approved by the Food and Drug Administration for bipolar treatment are summarized in Table 1. Lithium and many anticonvulsants are often also referred to as “mood stabilizers” based on their intended treatment effect rather than the drug’s mechanism. Given the chronic, relapsing/remitting course of bipolar disorder and the need for maintenance treatment in many patients, drugs begun for an acute mood episode (including mania) are often carried forward as maintenance treatment.

Table 1. FDA-approved medications for bipolar disorder

Drug Type	Generic Name First Date Approved	FDA –Listed Trade Name (Pharmaceutical Co.)	Manic	Mixed (Mania/ Depression)	Mainte- nance	Depression
Salts	Lithium 1970		X		X	
Atypical Antipsychotics	Aripiprazole 2004	Abilify (Otsuka)	X	X	X	
	Asenapine 2015	Saphris (Organon Sub Merck)	X	X		
	Cariprazine 2015	Vraylar (Forest)				
	Lurasidone 2013	Latuda (Sunovion Pharms)				X
	Olanzapine* 2000	Zyprexa (Lilly)	X	X	X	
	Olanzapine/fluoxetine combination* 2012	Symbyax (Lilly)				X
	Quetiapine 2004	Seroquel (AstraZeneca)	X			X
	Risperidone 2003	Risperdal (Janssen Pharm)	X	X		
	Ziprasidone 2004	Geodon (Pfizer)	X	X		
Anticonvulsants	Carbamazepine* 2004	Carbetrol (Shire), Epitol (TEVA), Equetro (Validus Pharms), Tegretol (Novartis), Teril (Taro)	X	X		
	Lamotrigine* 2003	Lamictal (GlaxoSmithKline)			X	
	Divalproex sodium* or valproate 1995	Depakote (ABBVIE)	X			
	Lamotrigine* 2003	Lamictal (GlaxoSmithKline)			X	

*Generic forms are available. FDA=Food and Drug Administration

Pharmacologic treatment is challenging. Some drugs that alleviate depression may increase the risk of mania, hypomania, or rapid cycling (four or more episodes in 12 months), while some drugs that alleviate acute mania may increase the risk of rebound depressive episodes. Based on changes in the DSM-5 criteria, in individuals with no prior bipolar disorder diagnosis, drug treatment induced manic and hypomanic episodes that last longer than expected pharmacological effects are now considered “true” episodes and count towards a bipolar

disorder diagnosis. All approved drugs have boxed warnings indicating serious or life-threatening risks.

Nonpharmacologic or psychotherapeutic techniques are applied to enhance medication adherence, reduce episode relapse (maintenance), and improve social and occupational functioning, which are often impaired during and after acute bipolar episodes. The majority of bipolar disorder-specific psychotherapeutic approaches have been studied in the last 15 years. These psychosocial approaches range from psychoeducational, cognitive behavioral, and family-focused, to interpersonal social rhythm therapy, and are administered both individually and in groups. Most psychotherapeutic approaches focus the treatment for individuals currently in the remission state of bipolar illness and often specifically exclude individuals currently in acute manic episodes.

Other nondrug treatment forms are based on physical approaches. They range widely from electroconvulsive therapy to treatments for circadian rhythms, such as light boxes, to acupuncture.

Scope and Key Questions

Several systematic reviews have assessed the effects of bipolar disorder treatment. Available reviews, however, do not incorporate the broad range of interventions (pharmacologic, psychosocial, other nondrug treatments) or necessarily target guideline developers with the specific intention of improving the treatment of bipolar disorder. This review provides a comprehensive up-to-date synthesis of the evidence on the effects of bipolar disorder treatments.

Key Questions

Key Question 1: What are the efficacy and comparative effectiveness of pharmacologic and nonpharmacologic treatments for adults with bipolar disorder?

- a. How do pharmacologic treatments (monotherapy or combination therapies) affect patient centered outcomes when compared with placebo?
- b. How do pharmacologic treatments (monotherapy or combination therapies) affect patient centered outcomes when compared with other active pharmacologic treatment?
- c. How do behavioral health treatments (psychotherapy, psychosocial interventions) affect patient centered outcomes when compared with usual care?
- d. How do behavioral health treatments (psychotherapy, psychosocial interventions, chronotherapy) affect patient centered outcomes when compared with other active treatment?
- e. How do somatic treatments (electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS)) affect patient-centered outcomes when compared with other active treatment?
- f. How do comprehensive programs affect patient centered outcomes when compared with usual care?

Key Question 2: What are the harms from pharmacologic and nonpharmacologic treatments for adults with bipolar disorder?

- a. What are the harms from pharmacologic treatments?
- b. What are the harms from behavioral health treatments?
- c. What are the harms from somatic treatments?
- d. What are the harms from comprehensive programs?

Key Question 3: What is the effectiveness of treatments to reduce the metabolic change (metabolic syndrome, glucose dysregulation, weight gain) side effects of first line pharmacologic treatments?

Key Question 4: Which patient characteristics predict the effectiveness and harms of pharmacologic and nonpharmacologic treatments for people with bipolar disorder, including disease-specific characteristics such as bipolar type, state severity, pediatric onset, new onset, treatment resistant, types of depression, and other comorbidities, and patient characteristics such as substance use, other psychiatric comorbidities, medical comorbidities, age, sex, race/ethnicity, socioeconomic status?

PICOTS

The Key Questions are further described with the populations, interventions, comparators, outcomes, timing, and settings (PICOTS) noted in Table 2.

Table 2. PICOTS

PICOT	Included	Excluded
Population	Adults, 18+ years old, with any bipolar disorder. Includes pregnant women	Pediatric patients with bipolar disorder Studies with samples of greater than 25% identified as schizoaffective disorder with bipolar –type symptoms. Schizoaffective disorder is distinguished by longer periods of psychotic symptoms than bipolar disorder. Major affective disorder not specifying unipolar depression versus bipolar disorder

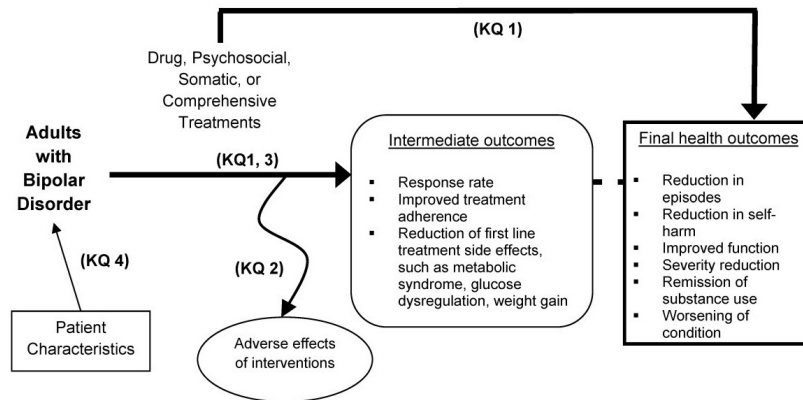
PICOT	Included	Excluded
Intervention	<p>Drug treatment Manic episodes – lithium, anticonvulsants, antipsychotics Depressive or mixed episodes – lithium, anticonvulsants, antipsychotics, antidepressants Maintenance state – lithium, anticonvulsants, antipsychotics, antidepressants Combination therapy – Two or more drugs begun simultaneously with similar therapeutic goal; Augmentation with a second drug to boost response when patient's symptoms have only partially remitted Two drugs with different goals (such as acute manic treatment added to maintenance drugs)</p> <p>Psychosocial treatment Individual or group psychotherapy Cognitive behavioral therapy (CBT) Family-focused therapy Interpersonal and social rhythm therapy Psychoeducation Chronotherapy</p> <p>Somatic treatment Electroconvulsive therapy (ECT) Transcranial magnetic stimulation (TMS)</p> <p>Comprehensive programs – multicomponent programs incorporating pharmacological, psychological, and social components in an integrated fashion.</p> <p>Interventions to reduce side effects of medications given for prolonged periods (metabolic syndrome, glucose dysregulation, weight gain) (such as verapamil, metformin)</p>	<p>Over-the-counter botanicals, nutritional supplements, dietary approaches (including omega 3)</p> <p>Programs designed primarily as improving drug adherence.</p>
Comparator groups	<p>Drug treatment – placebo, active comparator</p> <p>Psychosocial or Somatic treatment – placebo/sham, usual care, or active comparator</p> <p>Comprehensive treatment – placebo or active comparator</p> <p>Interventions – placebo, waitlist, active comparator, usual care</p>	

PICOT	Included	Excluded
Outcomes	<p>Final health or patient-centered outcomes:</p> <ul style="list-style-type: none"> Reduction of episodes outcomes Remission/Prevention of episodes Increased time between episodes/Time to remission Reduced hospitalization Reduction in self-harm Reduction in suicide Reduction in suicidal thoughts or self-harming behaviors Improved function Improved social and occupational functioning Change in disability Health related quality of life Severity reduction Remission of co-occurring substance use disorder Worsening of condition <p>Intermediate outcomes</p> <ul style="list-style-type: none"> Treatment response Improved treatment adherence Reduction of first line treatment side effects (metabolic syndrome, glucose dysregulation, weight gain) <p>Adverse effects of interventions</p> <ul style="list-style-type: none"> Switching states Increase metabolic syndrome, glucose dysregulations, weight gain Reported adverse effects 	<p>Time to drug effect</p> <p>Drug tolerance studies; phase II studies</p> <p>All other intermediate outcomes, such changes in physiologic conditions</p>
Timing	<p>Acute mania/mixed episode: at least 3 weeks treatment duration plus post-treatment followup (if any)</p> <p>Acute depression: at least 3 months treatment duration plus post-treatment followup (if any)</p> <p>Maintenance: at least 6 months treatment duration plus post-treatment followup (if any)</p>	
Setting	Inpatient and outpatient for mania or mixed episodes, depression. Outpatient for depression or maintenance (inpatient start allowed).	

PICOTS=Population, interventions, comparators, outcomes, timing, settings

Analytic Framework

Figure 1. Analytic framework for treatment for bipolar disorder



KQ=Key Question

Report Organization

As indicated by the structure of our Key Questions, we had originally planned to provide results for bipolar disorder subpopulations important to clinicians. However, we found that such detail was not forthcoming. Thus, rather than organizing the report by Key Question, this report presents the benefit and harms results organized by type of treatment. [Chapter 4](#) gives results for drug treatments for mania. The chapter presents benefits and harms for antipsychotics, each drug first as monotherapy, then, if present, in combination with mood stabilizers, followed by results for mood stabilizers alone, and then other drugs. [Chapter 5](#) presents benefits and harms for drug treatments for depression, [Chapter 6](#) for maintenance treatment, and [Chapter 7](#) for psychosocial therapies and other nondrug treatments. Since we were unable to provide information on subpopulations, we provide tables with details of the treated populations for each intervention. Each of the results chapters also includes a short discussion section for issues strictly related to the chapters' results. An overall discussion of themes cutting across all the chapters is provided in [Chapter 8](#).

Chapter 2. Methods

The methods for this Comparative Effectiveness Review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>); certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.¹⁰ This section summarized the methods used.

Topic Refinement and Review Protocol

This report topic and preliminary Key Questions arose through a public process. Initially a panel of key informants, involving psychiatrists, psychologists, researchers, consumer advocates, and consumers, gave input on the Key Questions and population, interventions, comparators, outcomes, and timing (PICOT) to be examined. Key Questions, PICOT, and the analytic framework were posted for public comment from December 19, 2013 to January 10, 2014. In response to comments provided, we made several changes. We then drafted a protocol for the CER and recruited a technical expert panel to provide high-level content and methodological expertise feedback on the review protocol. The protocol was posted June 23, 2014 at <https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1926>.

Literature Search Strategy

We searched Ovid Medline, Ovid PsycInfo, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify previous randomized controlled trials and prospective cohort studies published and indexed in bibliographic databases. Our search strategy, which appears in [Appendix A](#), included relevant medical subject headings and natural language terms for the concept of bipolar disorder. This concept was combined with filters to select randomized controlled trials (RCTs), observational studies, and systematic reviews. Dates for the search algorithm were 1994 to May 2017. We anticipated that older, established treatments would be covered by prior reviews, and we supplemented our searches with backward citation searches of relevant systematic reviews.

We conducted additional grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and Food and Drug Administration databases. We searched ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP) for ongoing studies. We also reviewed Scientific Information Packets (SIPs) sent by manufacturers of relevant interventions. Grey literature search results were used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and inform future research needs.

Studies were included in the review based on the PICOTS framework outlined in Table 2 and the study-specific inclusion criteria described in Table 3.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Studies that enroll adults with any form of bipolar disorder (bipolar I, bipolar II, bipolar otherwise specified, bipolar not otherwise specified, rapid cycling) using any diagnostic process. Studies that enroll bipolar disorder patients along with other patients with DSM-V diagnoses were included if the patients with bipolar disorder are analyzed separately.
Study Design and Quality	RCTs, nonrandomized controlled trials, and prospective cohort studies for each population and treatment option. Studies must have at least 10 participants per arm at the first relevant outcome period. Except for studies reporting time to relapse as a primary outcome (generally maintenance studies), Studies for acute mania or depression treatments with greater than 50% attrition were excluded for fatally high risk of bias. Follow-on studies of those excluded RCTs were also excluded. Studies with greater than 50% attrition in the treatment arm were excluded if the control arm did not incorporate some form of placebo or attention control; the lack of such comparators creates a situation where the control arm would not be subject to forces prompting a participant to withdraw from a study. Studies for maintenance treatments with greater than 50% attrition were retained only if time to relapse outcomes were available, and then only those outcomes and withdrawal information were includable. Prospective cohort studies must include a comparator and appropriate methods to correct for selection bias. Observational studies that do not adequately report study information to allow the abstraction of time sequences for treatment and followup duration or have indeterminable numerators and denominators for outcomes and adverse event rates were excluded at the abstraction phase.
Time of Publication	1970 and forward for trials of pharmacologic and somatic treatments. Lithium was FDA approved in 1970. 1994 and forward for all other literature. This corresponds with the period during which systematic reviews and evidence-based research approaches have been applied to behavioral health.
Publication type	Published in peer reviewed journals
Language of Publication	English

DSM-5=Diagnostic and Statistical Manual for Mental Disorders, 5th Edition; FDA=Food and Drug Administration;
RCT=randomized controlled trial

We reviewed bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. All studies identified at title and abstract as relevant by either of two independent investigator underwent full-text screening. Two investigators independently performed full-text screening to determine if inclusion criteria were met. Differences in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator.

Risk of Bias Assessment of Individual Studies

Risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design. For RCTs, questionnaires developed from the Cochrane Risk of Bias¹¹ tool were used. We developed an instrument for assessing risk of bias for observational studies based on the RTI Observational Studies Risk of Bias and Precision Item Bank¹² ([Appendix B](#)). We selected items most relevant in assessing risk of bias for this topic, including participant selection, attrition/incomplete outcome data, ascertainment of group assignment, and appropriateness of analytic methods. Study power was assessed in ‘other sources of bias’ in studies with data that were not eligible for pooling. For psychosocial intervention, the presence of treatment fidelity, that is, treatment definition and implementation, was also evaluated. Overall summary risk of bias assessments for each study were classified as

low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results were believable given the study's limitations. When the two investigators disagreed, a third party was consulted to reconcile the summary judgment.

Data Extraction

For studies meeting inclusion criteria, one investigator abstracted relevant data into extraction forms created in Excel. Evidence tables were reviewed and verified for accuracy by a second investigator. Data fields included author, year of publication, setting, subject inclusion and exclusion criteria, intervention and control characteristics (intervention components, timing, frequency, duration), followup duration, participant baseline demographics, comorbidities; method of diagnosis, enrollment, and severity, descriptions and results of primary outcomes, adverse effects, study withdrawals, and study funding source.

For outcomes, only overall scale scores were reported for all measurement scales; subscales or individual items from scales were not abstracted. Abstracted outcomes included:

- Responders and/or remitters (for acute states) number and/or time to relapse (for maintenance), including definitions used in the studies,
- Symptoms scales; only one scale per state per study, following a “most reported” hierarchy,
- Global functioning (including social performance and quality of life for psychosocial studies),
- Utilization, such as emergency department use,
- Change in self-harm behaviors, including suicidality,
- Withdrawals; overall, due to lack of effect, and due to side effects,
- Serious adverse events; rates of extrapyramidal symptoms, switching, and weight gain of > 7 percent.

Adverse events were treatment emergent, not treatment-related events. Harms were chosen based on an informal prioritization process with the help of the Technical Expert Panel (TEP). We focused on patient-centered harms and not on those that were already well-established.

For maintenance studies reporting time to relapse as the primary outcome but with greater than 50 percent attrition, only summary measures of time to relapse, overall withdrawal, withdrawal due to adverse events and adverse events were abstracted. We did not abstract symptom scales due to loss of participants over time. Time to relapse for any mood episode was primary unless the study was designed for a specific episode type; for example, the primary outcome of time to next depressive episode for bipolar II patients stabilized from depression.

As a courtesy to readers, we also abstracted limited information on studies excluded for greater than 50 percent attrition: study design, enrollment, intervention, and comparison (available in [Appendix D](#)).

Data Synthesis

We summarized the results into evidence tables and synthesized evidence for each unique population, comparison, and outcome combination. We emphasized patient-centered outcomes in the evidence synthesis. Results are organized by bipolar type and state (such as acute mania, acute depression, or euthymia). Where available, results by population subgroups were also provided. We used statistical differences between groups to assess effects. For outcomes with well-established minimum important differences (MIDs), we used the MID to aid interpretation.

[Appendix C](#) provides a list of outcomes used in the available literatures, with associated MIDs where available.

Decisions for pooling were based on the homogeneity of study populations using inclusion criteria, specific interventions, and the ability to treat outcome measures as similar. When pooling was possible, we conducted meta-analyses using the random effects modeling approach. Continuous outcomes were summarized with precision-weighted mean differences (WMD) and/or standardized mean differences (SMD) and 95 percent confidence intervals (CIs). In our context, these were generally difference in difference estimates from each study. If a study did not report a standard error for the difference in difference estimate, we calculated it from a P-value or CI and the appropriate degrees of freedom. If neither a CI nor an exact P-value was given but an upper bound for the P-value was, e.g., < 0.05 , we used that to calculate an upper bound of the standard error. If the degrees of freedom of the relevant t-distribution was not given, we attempted to back it out of the study based upon the statistical methods that were used as long as we could confidently conclude that it was greater than 25. Binary outcomes were summarized with precision-weighted log odds ratios (OR) and 95 percent CIs.

We used the restricted maximum likelihood estimator (REML) of the heterogeneity variance because, although simulation studies have shown it to suffer from negative bias¹³, it has generally performed comparatively well with regards to mean-square error¹⁴. We also used the Knapp-Hartung adjustment in order to avoid the potentially high inflation of the type-I error rate that can arise when dealing with small numbers of even moderately heterogeneous studies.^{15, 16} We chose not to perform meta-analyses when only two studies were available to pool as, in this context, application of the Knapp-Hartung adjustment can diminish power to trivial levels and standard approaches can easily suffer from extreme inflation of type-I error.¹⁷

As a sensitivity analysis, we also performed all meta-analyses using fixed-effect models. These results are charitably interpreted as providing an estimate of the true average effect among completed trials and are presented along with the results derived from analyses using random-effect models.¹⁸ However, we base our main conclusions on the random-effects set of results. All analyses were performed with R software¹⁹, using the metaphor package.¹⁸

We assessed the clinical and methodological heterogeneity to determine appropriateness of pooling data.²⁰ When pooling was not appropriate due to lack of comparable studies or heterogeneity, qualitative synthesis was conducted.

Studies were grouped by treatment, bipolar type and/or bipolar state. Phases were grouped as: (1) acute mania or hypomania, including mixed, (2) acute depression, (3) any acute state (often for psychosocial maintenance studies), (4) euthymic or subsyndromal (generally for maintenance studies), and (5) nonspecific, that is, either euthymic, acute in any episode, or post-hospitalization (these studies stated essentially any patient with bipolar disorder except acute mania). For drug studies treating patients for residual symptoms, patients were classified as nonresponders to standard treatment (usually noted in adjunctive drug studies). Studies were categorized as maintenance studies if the study inclusion criteria did not specify an acute episode at study entry.

Study outcomes were grouped by treatment duration or followup period. For acute mania treatment, outcomes were grouped by 3-4 weeks and then final measurement (generally 6 to 12 weeks) if available. Depression treatment studies are reported at 3 months and final endpoint. Maintenance study outcomes are reported at 6 months, 8-12 months, and “prolonged followup” of the final endpoint.

Comparators for psychosocial studies were grouped as inactive (usual care or standardized care) or active (active head to head comparisons of psychosocial therapies including supportive therapy).

We conducted several sensitivity analyses where possible. In forest plots, outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, were presented in grey scale.

Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence for primary outcomes within each comparison were evaluated based on four required domains: (1) study limitations (risk of bias); (2) directness (a single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).²¹ A fifth domain, reporting bias, was assessed when strength of evidence based upon the first four domains is moderate or high.²¹ Based on study design and conduct, study limitations were rated as low, moderate, or high. Consistency was rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness was rated as either direct or indirect. Precision was rated as precise or imprecise. Assessing strength of evidence for studies with null findings is especially challenging because several domains are designed to address differences. Although it is important to assess the strength of evidence for null findings (i.e. intervention and comparison yielded results that were not statistically different from each other), it is difficult. It is hard to assess effect size when there is no effect in studies that test for superiority; how does one establish a level of precision that provides confidence of no effect? This is especially true when populations, interventions, and comparators are not consistent, as is the case with much of the nondrug literature. We also downgraded precision when there was considerable attrition that was addressed through last-observation carried forward methods. Due to the large number of comparisons with findings of no effect, we assessed strength of evidence and formulated results cautiously. Based on these factors, the overall evidence for each outcome was rated as:²¹

High: Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.

Moderate: Moderately confidence that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.

Low: Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.

Insufficient: No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

We assessed strength of evidence for validated scales (such as the Beck Depression Inventory, Young Mania Rating Scale, Hamilton Depression Rating Scale, Clinical Global Improvement Scale) and commonly used items that examine improved function (such as the Functional Assessment Short Test). We did not assess strength of evidence for less commonly measured items such as increased time between episodes or hospitalizations. Attempted suicide and other self-harming behaviors were also not assessed for strength of evidence due to the difficulty of defining and measuring such behaviors.

Applicability

Applicability of studies was determined according to the PICOTS framework. Bipolar research generally draws from highly defined populations, resulting in samples that are often drawn from subpopulations rather than the bipolar populations at large. Thus, the ability to infer generalizability can be compromised. Applicability also deals with transportability of evidence for the type of treatment—level of treatment, treatment fidelity, skills of treatment agent, setting (and measurement)—and its fit to a particular treatment setting. Study characteristics that may affect applicability include, but are not limited to, the population from which the study participants are enrolled, diagnostic assessment processes, narrow eligibility criteria, and patient and intervention characteristics different than those described by population studies of bipolar disorder.²² These applicability issues are present in the synthesis frameworks and sensitivity analyses described in more detail in the data synthesis section.

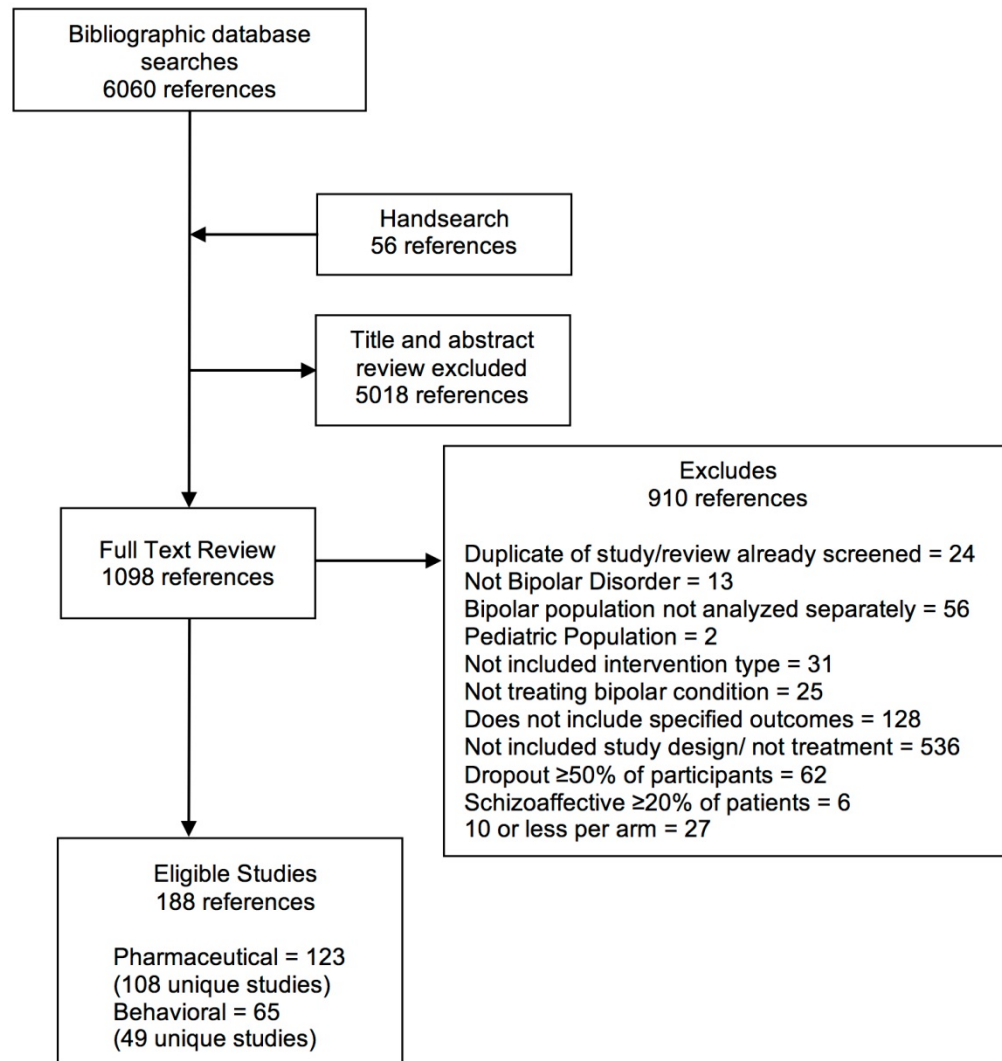
Peer Review and Public Commentary

Experts in bipolar disorder and systematic reviews were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We addressed all reviewer comments, revised the text as appropriate, and documented all responses in a disposition of comments report made available within 3 months of the Agency posting the final systematic review on the Effective Health Care website.

Chapter 3. Search Results

We identified 6060 unique citations (Figure 2) to May 2017 from bibliographic databases addressing drug, psychosocial, or other nondrug treatments for bipolar disorder (BD). Fifty-six articles were added through hand search. An initial title and abstract review excluded 4,971 articles that were not related to drug or nondrug treatments for patients with BD. Full texts of 1,145 articles were reviewed to determine final inclusion. [Appendix D](#) provides a list of articles excluded at full text.

Figure 2. Literature flow diagram



We identified 188 unique publications eligible for inclusion, including 123 studies of drug treatments and their associated harms, and 65 focused on psychosocial and other physical treatments. An additional 62 publications, 57 drug and 5 psychosocial, were excluded for attrition greater than 50 percent; brief abstracts of these studies are provided in [Appendix D](#).

Drug studies examined 28 separate drugs that were tested against 14 different types of comparators. These treatments and their comparators may have been single drug therapies or combination therapies of multiple drugs tested against either monotherapies or other multiple drug therapies. These then separated into 103 treatment comparisons, 59 of which had only one study contribute information. For Key Question 3, we found no studies meeting inclusion criteria that looked at treatments to reduce metabolic change side effects of drug treatments. Table 4 breaks the included studies down into each individual comparison for drug studies. Only five comparisons had four or more studies contributing. The populations tested in drug studies were overwhelmingly bipolar disorder I (BD-I) patients.

Table 4. Eligible unique studies by drug intervention and comparator

Report Section	Treatment	Comparator	Number Unique Studies	Number Unique Studies Not Solely BD I Population
Antipsychotics for Acute Mania (Chapter 4)	Aripiprazole	Placebo	3	
		Haloperidol	2	
	Aripiprazole + Lithium/Divalproex /Valproate	Placebo + Lithium/Divalproex /Valproate	2	
	Aripiprazole + Valproic Acid	Haloperidol + Valproic Acid	1	
	Asenapine	Placebo	3	
		Olanzapine	2	
	Asenapine + Lithium/Valproate	Placebo + Lithium/Valproate	1	
	Cariprazine	Placebo	3	
	Haloperidol	Placebo	2	
	Olanzapine	Placebo	5	
		Haloperidol	1	
		Lithium	3	1 NR
		Risperidone	1	
		Divalproex/ Valproate	4	
	Olanzapine + Lithium	Chlorpromazine + Lithium	1	
	Olanzapine + carbamazepine	Placebo + Carbamazepine	1	
	Olanzapine + Divalproex	No Placebo + Divalproex	1	
	Olanzapine + Valproate	No Placebo + Valproate	1	
	Olanzapine + Lithium/Valproate	Placebo + Lithium/Valproate	1	
	Quetiapine	Placebo	5	1 BD I, II, NOS
		Haloperidol	1	
		Lithium	2	
	Quetiapine + Lithium or Divalproex	Placebo + Lithium or Divalproex	2	
	Risperidone	Placebo	2	
		Haloperidol	2	
		Lithium	1	
	Risperidone + Mood Stabilizer	Placebo + Mood Stabilizer	1	
	Ziprasidone	Placebo	2	
	Ziprasidone + Lithium or Divalproex	Placebo + Lithium or Divalproex	1	
Mood Stabilizer for Acute Mania (Chapter 4)	Carbamazepine	Placebo	1	
		Lithium	2	
		Valproate	1	
	Divalproex	Placebo	2	
	Lamotrigine	Lithium	1	
	Lithium	Placebo	2	

Report Section	Treatment	Comparator	Number Unique Studies	Number Unique Studies Not Solely BD I Population
Other Drugs Not FDA-Approved for Acute Mania (Chapter 4)		Haloperidol	1	
		Valproate	1	
	Olanzapine +Valproate	No placebo +Olanzapine	1	
	Allopurinol + Lithium/Treatment As Usual/Valproate	Placebo + Lithium/Treatment As Usual/Valproate	3	
	Allopurinol + Valproate/ psychotropic medications	Placebo + Valproate/ psychotropic medications	1	
	Celecoxib	Placebo	1	
	Dipyridamole + Lithium	Placebo + Lithium	1	
		Allopurinol + Lithium	1	
	Donepezil + Lithium	Placebo + Lithium	1	
	Gabapentin + Lithium	Placebo + Lithium	1	
	Paliperdone ER	Placebo	2	
		Quetiapine	1	
	Paliperdone ER	Olanzapine	1	
	Paliperdone ER + Lithium or Valproate	Placebo + Lithium or Valproate	1	
	Tamoxifen	Placebo	1	
	Endoxifen (tamoxifen derivative)	Divalproex	1	
	Topiramate	Placebo	1	
		Lithium	1	
	Topiramate + Lithium/Divalproex	Placebo + Lithium/Divalproex	1	
	Topiramate + Risperidone	Divalproex + Risperidone	1	
Treatment for Acute Depression (Chapter 5)	Antidepressant SSRI (paroxetine or bupropion) + Mood Stabilizer and/or Psychosocial Interventions	Placebo + Mood Stabilizer and/or Psychosocial Interventions	1	1 BD I, II
	Lamotrigine + Lithium or Divalproex	Placebo + Lithium or Divalproex	1	1 BD I, II
	Memantine + Valproic Acid	Placebo + Valproic Acid	1	1 BD II only
	Sertraline + Lithium	Lithium	1	1 BD II only
		Sertraline	1	1 BD II only
	Venlafaxine	Lithium	2	2 BD II only
	Lithium + Optimal Personalized Treatment	No Placebo + Optimal Personalized Treatment	1	1 BD I, II
Maintenance Treatments (Chapter 6)	Aripiprazole (injectable)	Placebo	1	
	Aripiprazole (oral)	Placebo	1	
	Aripiprazole + Lamotrigine	Placebo + Lamotrigine	1	
	Aripiprazole + Lithium/Divalproex /Valproate	Placebo + Lithium/Valproate	2	
	Carbamazepine	Lithium	2	2 BD I, II
	Fluoxetine	Placebo	1	1 BD II
		Lithium	1	1 BD II
	Gabapentin + Lithium and/or Divalproex and/or Carbamazepine	Placebo + Lithium and/or Divalproex and/or Carbamazepine	1	1 BD I, II
	Lamotrigine	Placebo	3	1 BD I, II
		Mood stabilizer discontinuation	1	1 BD I, II, NOS
		Lithium	2	
	Lithium	Placebo	6	
	Lithium + Valproate	Lithium	1	
		Valproate	1	

Report Section	Treatment	Comparator	Number Unique Studies	Number Unique Studies Not Solely BD I Population
	Olanzapine	Placebo	2	
		Divalproex	1	
		Lithium	1	
	Olanzapine + Lithium or Valproate	Placebo + Lithium or Valproate	1	
	Oxcarbazepine + Lithium	Placebo + Lithium	1	1 BD I, II
	Perphenazine + Lithium or Carbamazepine or Valproate	Placebo + Lithium or Carbamazepine or Valproate	1	
	Quetiapine	Placebo	1	
		Lithium	1	
	Quetiapine + Lithium or Divalproex	Placebo + Lithium or Divalproex	2	
	Quetiapine + Adjunctive Personalized Treatment	Lithium + Adjunctive Personalized Treatment	1	1 BD I, II
	Risperidone	Placebo	2	
		Olanzapine	1	
	Risperidone + Treatment as Usual	Placebo + Treatment as Usual	1	1 BD I, II
		No Placebo + Treatment as Usual	1	1 BD I, II
	Valproate	Lithium	1	
	Divalproex	Placebo	1	
		Lithium	2	1 BD I, II
	Divalproex + Lithium	Placebo + Lithium	1	1 BD I, II
	Valproic Acid + Aripiprazole	Lithium + Aripiprazole	1	
	Venlafaxine	Lithium	1	1 BD II
	Ziprasidone + Lithium or Divalproex	Placebo + Lithium or Divalproex	1	

BD=bipolar disorder; ER=extended release; FDA=Food and Drug Administration; NR=not reported; NOS=not otherwise specified

Nondrug studies examined eight therapy approaches, seven of which were psychosocial intervention types: 1) psychoeducation, 2) cognitive behavioral therapy (CBT), 3) systematic/collaborative care, 4) family/partner interventions, 5) interpersonal and social rhythm therapy (IPSRT), 6) combination treatments (treatments that combined two or more psychosocial interventions, and 7) other psychosocial treatments (e.g. self-management via phone application support). A somatic therapy intervention, repetitive transcranial magnetic stimulation (rTMS), was examined as a nonpsychosocial, nondrug intervention. Each study represented a unique comparison due to differences in the structure of each intervention and control/comparator groups.

Table 5 provides the included studies for each individual comparison for nondrug studies. Comparators are categorized as inactive (e.g., usual care, no intervention) or active (e.g., a different psychosocial therapy, peer support) to indicate whether the studies were measuring the efficacy or effectiveness of the intervention. Since the nondrug studies were not as clearly delineated by BD states, the table further breaks down the studies by study enrollment criteria. For example, some studies may have required a particular BD state while other studies accepted BD participants in any state while still others may have excluded participants with a specific state.

Table 5. Eligible unique studies by nondrug intervention and comparator

Treatment	Comparator	Mania	Depression	Euthymic	Any State	Non-manic	Current Episode*	Hypo - manic
Psychoeducation	Inactive	0	0	8	2	0	0	0
	Active	0	0	2	1	0	0	0
CBT	Inactive	0	0	6	3	0	0	0
	Active	0	0	4	0	1	0	0
Systematic or Collaborative Care	Inactive	0	0	2	5	0	0	0
Family or Partner Interventions	Inactive	0	0	1	0	0	1	0
	Active	1	0	0	2	0	1	0
IPSRT	Inactive	0	0	0	0	0	1	0
	Active	0	0	0	0	0	0	1
Combination Therapy**	Inactive	0	0	1	2	0	0	0
	Active	0	0	1	1	0	0	0
Other Psychosocial	Active	0	1	0	1	0	0	1
Somatic Therapy	Inactive	0	1	0	0	0	0	0

*Current episode means the enrolled participants may be currently experiencing any form of mania or depression, therefore not in a euthymic state. **Intervention is a combination of two or more psychosocial therapies.

CBT=cognitive behavioral therapy; IPSRT=interpersonal and social rhythm therapy

Chapter 4. Drug Treatments for Acute Mania

We identified 71 publications of 67 unique studies for acute mania that examined 28 separate drugs tested against 14 different comparators. These treatments and their comparators may have been single drug therapies or combination therapies of multiple drugs tested against either placebo monotherapies or other multiple drug therapies. The 67 studies combined into 56 treatment comparisons, 35 of which had only one study contribute information. Only three comparisons had four or more studies contributing. An additional 54 studies were excluded due to attrition higher than 50 percent.

The high attrition studies (greater than 50% were excluded because observed results among patients who complete a trial may not generalize to the entire patient population of interest if systematic differences between patients who do not complete the study and those who do (i.e., attrition is not random and/or likely due to bipolar disorder (BD) or treatment-relevant factors) occur. Moreover, if there are differential rates of attrition across study arms, or even similar rates but a different distribution of reasons for attrition, primary effect estimates and statistical inference can suffer from bias, potentially severe. The Last Observation Carried Forward (LOCF) method—by far the most common method used to address missing outcome data in the included studies—requires an assumption that the health-status of patients who dropped out of the trial would not have changed had future observations been recorded. This is a particularly heroic assumption in the context of withdrawal due to lack of efficacy or adverse events, not uncommon occurrences in the context of pharmaceutical treatment of patients with BD.²³ When this assumption is inappropriate, use of LOCF methods can bias effect estimates. Moreover, estimates of standard errors will understate the true uncertainty surrounding effect estimates due to the added uncertainty of having to impute data, leading readers to believe the result is more precise than it actually is and potentially inflating the type-I error rate.²⁴ This potential bias in the estimates of effect is even more problematic in studies with greater than 50 percent attrition that require imputing half or more of the data.

The results in this chapter for treatments for acute mania are organized by general drug category: antipsychotics, mood stabilizers, and drugs otherwise not specified. Within the antipsychotics section, results are presented by specific drug, then broken into single drugs compared to placebo or another drug, then, when appropriate, drug in combination with mood stabilizers compared to placebo or another drug. Likewise, the mood stabilizers and other drugs sections are presented first by single drug results followed by combination therapy results.

Antipsychotic Drugs for Acute Mania

Key Points

- Most antipsychotic drugs had few studies to contribute to findings. Studies for antipsychotics plus mood stabilizers were even more sparse and scattered.
- Low-strength evidence shows improved mania symptoms for all Food and Drug Administration (FDA)-approved antipsychotics, except aripiprazole, when compared to placebo for adults with bipolar I disorder (BD-I). For four of the antipsychotics we were able to provide a point estimate. However, most manic symptom improvements were of modest clinical significance, with values that were less than the minimally important difference (MID) but still large enough that a reasonable proportion of participants likely received a benefit.

- Low-strength evidence showed no statistical differences in acute mania symptoms between olanzapine and divalproex/valproate.
- The ability to draw stronger conclusions for antipsychotics was hindered by high attrition rates.
- Evidence was insufficient to draw conclusions regarding antipsychotic drugs alone compared to placebo or antipsychotic drugs plus mood stabilizers compared with another drug for BD-I for the primary outcomes of interest (response, symptom scores, and function).
- When reported, all comparisons tended to show no differences between groups in serious adverse events. Participants using atypical antipsychotics, except quetiapine, reported experiencing more extrapyramidal symptoms compared to placebo. Participants using haloperidol reported experiencing more extrapyramidal symptoms compared to other antipsychotics. Participants using olanzapine reported experiencing more clinically significant weight gain.

Eligible Studies for Antipsychotics

Eight antipsychotic drugs were examined in 47 publications of 43 unique studies for BD patients experiencing acute manic events. Of these, seven are FDA approved for use in adults with BD experiencing mania: aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone. An additional unpublished study for aripiprazole plus mood stabilizers was also included for metaanalysis. Haloperidol, an antipsychotic treatment available since the late 1950's and a World Health Organization listed essential medicine, was FDA approved in 1986 for schizophrenia (not for mania in adults with BD). All were examined as single drugs and all but cariprazine were also examined as a treatment combined with mood stabilizers. The populations tested were BD-I patients, which is understandable given the BD-I diagnosis requires history of just one episode of mania. Only one study (for quetiapine) included adults with bipolar II disorder (BD-II) or bipolar disorder not otherwise specified (BD-NOS). No studies specifically assessed drug effectiveness in treatment of hypomania. The large majority of studies with usable outcomes were measured at 3 weeks duration.

[Appendix E](#) provides detailed evidence tables, summary risk of bias assessments, forest plots when appropriate, and assessments of strength of evidence for key comparisons and outcomes. A summary of findings with at least low-strength evidence for drug treatments for acute mania are provided in Table 6. Any intervention and comparison not listed in Table 6, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 6. Summary of findings with at least low-strength evidence for antipsychotic drug treatments for acute mania

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Asenapine vs. placebo	3 RCT ^{25, 26 27} (n=936) 3 weeks	Response/Remission Rates: No difference YMRS: Favors Asenapine, MD 4.37 (95% CI 1.27, 7.47; MID 6) CGI-BP-S: Favors Asenapine, MD 0.5 (95% CI 0.29, 0.71; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Cariprazine vs. placebo	3 RCT ^{28 29 30} (n=1,047) 3 weeks	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT=5.6 Remission Rate: Favors Cariprazine, OR 1.95 (95% CI 1.45, 2.63); NNT= 7 YMRS: Favors Cariprazine, MD 5.38 (95% CI 1.84, 8.92; MID 6) CGI-BP-S: Favors Cariprazine, MD 0.54 (95% CI 0.35, 0.73; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference	Low (moderate study limitations, imprecise)
Olanzapine vs. placebo	5 RCT ^{31 32 26 33 34} (n=1199) 3 weeks	Response Rate: Favors Olanzapine, OR 1.99 (95% CI 1.29, 3.08); NNT 6 Remission Rate: Favors Olanzapine, OR 1.75 (95% CI 1.19, 2.58); NNT 7.5 YMRS: Favors Olanzapine, MD 4.9 (95% CI 2.34, 7.45; MID 6) Withdrawal (Lack of Efficacy, Overall): Favors Olanzapine, MD 0.42 (95% CI 0.29, 0.61)	Low (moderate study limitations, imprecise)
	3 RCT ^{31 33 34} (n=611) 3 weeks	CGI-BP-S: No difference	Low (moderate study limitations, imprecise)
Quetiapine vs. placebo	4 RCT ^{35 36 37, 38} (n=1,007) 3 weeks	Response Rate: Favors Quetiapine, OR 2.07 (95% CI 1.39, 3.09); NNT 6.2 Withdrawal (Lack of Efficacy): Favors Quetiapine, MD 0.38 (95% CI 0.23, 0.63)	Low (moderate study limitations, imprecise)
	5 RCT ^{35 36 37 38 39} (n=699) 3 weeks	YMRS: Favors Quetiapine, MD 4.92 (95% CI 0.31, 9.53; MID 6)	Low (moderate study limitations, imprecise)
	5 RCT ^{35 36 37 38 39} (n=806) 3 weeks	CGI-BP-S: Favors Quetiapine, MD 0.54 (95% CI 0.35, 0.74; MID 1)	Low (moderate study limitations, imprecise)
Risperidone vs. placebo	2 RCT ^{40 41} (n=584) 3 weeks	Response Rate, YMRS, and CGI: Favors Risperidone (not pooled)	Low (moderate study limitations, imprecise)
Ziprasidone vs. placebo	2 RCT ^{42, 43} (n=402) 3 weeks	Response Rate, YMRS, and CGI: Favors Ziprasidone (not pooled)	Low (moderate study limitations, imprecise)
Olanzapine vs. Divalproex/ Valproate	2 RCTs ^{44 33} (n=635) 3 weeks	Response and Remission: No difference	Low (moderate study limitations, imprecise)
	3 RCTs ^{33, 44, 45} (n=750) 3 weeks	YMRS: No difference	Low (moderate study limitations, imprecise)
	3 RCTs ^{33, 44, 45} (n=578) 3 weeks	CGI: No difference	Low (moderate study limitations, imprecise)

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
	4 RCTs ^{33, 44-46} (n=867) 3 weeks	Withdrawals: No difference	Low (moderate study limitations, imprecise)

AE=adverse events; CGI =Clinical global impression; CI=confidence interval; CGI-BP=Clinical global impression scale, bipolar edition; MD=mean difference; MID=minimally important difference; n=number; NNT=number needed to treat; OR=odds ratio; RCT=randomized controlled trial; YMRS=Young mania rating scale

Aripiprazole

We identified four unique randomized controlled trials (RCTs) of aripiprazole,⁴⁷⁻⁵⁰ and two eligible publications reporting two unique RCTs of aripiprazole plus mood stabilizers for acute mania with at least 3 weeks followup.^{51, 52} Three studies were assessed as moderate risk of bias and three were assessed as high. An additional 6 studies were excluded for attrition over 50 percent.⁵³⁻⁵⁸ All studies were funded by industry. Three studies compared aripiprazole to placebo⁴⁸⁻⁵⁰ and two compared to haloperidol.^{47, 48} Sample sizes ranged from 42 to 485 participants, and all participants were BD-I. One unpublished RCT was discovered—clinicaltrials.gov ID: NCT00046384—which compared aripiprazole with placebo, with a total of less than 60 patients. The trial was prematurely closed and allegedly did not produce results.

Aripiprazole Alone

Table 7 summarizes the population and major inclusion and exclusion criteria for each aripiprazole study for acute mania. [Appendix E](#) provides further detail.

Table 7. Population and inclusion criteria for studies of aripiprazole alone for acute mania

Author, Year Single/Multisite Location Risk of Bias (ROB) PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Kanba, 2014 ⁴⁹ Multisite Asia High ROB 22540407	I: Aripiprazole C: Placebo	BD-I; DSM-IV	Mean Age 38 (18-75) 59% Female Race NR N = 247	Manic/Mixed episode; YMRS ≥ 20; Current episode <4 weeks	First Manic Episode Schizoaffective Neurological Disorders Other Mental Health Substance Abuse Pregnant/Nursing
Young, 2009 ⁴⁸ Multisite All Continents Moderate ROB 19118324	I: Aripiprazole C1: Placebo C2: Haloperidol	BD-I; DSM-IV	Mean Age 41 (18-76) 56% Female 78% White N = 485	Manic/Mixed (with/without psychotic features) in acute relapse; YMRS ≥ 20 and MADRS ≤ 17 at baseline, <25% decrease in YMRS score and ≤4 point MADRS score between screening and baseline visits; Current episode <3 weeks	First Manic Episode Schizoaffective Neurological Disorders Other Mental Health Taking Other Meds Substance Abuse

Author, Year Single/Multisite Location Risk of Bias (ROB) PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Vieta, 2005 ⁴⁷ Multisite NR Moderate ROB 16135860	I: Aripiprazole C: Haloperidol	BD-I; DSM-IV	Mean Age 42 (NR) 62% Female Race NR N = 347	Manic/Mixed episode; YMRS ≥ 20; Current episode <4 weeks	Other Mental Health Taking Other Meds Substance Abuse
Sachs, 2006 ⁵⁰ Multisite North America High ROB 16401666	I: Aripiprazole C: Placebo	BD-I; DSM-IV	Mean Age 39 (NR) 51% Female 92% White N = 272	Manic/Mixed episode; YMRS ≥ 20; Current episode <4 weeks	First Manic Episode Schizoaffective Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=risk of bias; YMRS=Young Mania Rating Scale

Aripiprazole Alone Versus Placebo

Evidence was insufficient for all outcomes from three studies (n=823) to address whether aripiprazole was better than placebo for acute mania in adults with BD-I, due to high study limitations and imprecise data.⁴⁸⁻⁵⁰ Following AHRQ methods, random effect models for pooling data, which allow one to extend the findings to the general population, largely showed no difference between groups in response rates, manic symptom improvement, or withdrawal rates. If fixed effect models are used, which only allows inferences for the specific participants in the specific studies, symptom improvements were seen. However, the improvement may not be clinically meaningful based on values that are less than the MID. The Young Mania Rating Scale (YMRS) mean difference of 3.85 (95% CI 2.27, 5.44) is less than the MID of 6, and the Clinical Global Improvement (CGI) score mean difference of 0.44 (95% CI 0.25, 0.63) is less than the MID of 1. There were no differences between groups for serious adverse events.

Aripiprazole Alone Versus Active Control

Evidence was insufficient for all outcomes from two studies (n=674) to address whether aripiprazole was better than haloperidol for acute mania in adults with BD-I, due to mostly high study limitations and imprecise data.^{47, 48} Studies reported no differences between groups for response or remission rates and mixed results as to which drug was favored. Akathisia and extrapyramidal symptoms were reported lower in participants using aripiprazole versus haloperidol; other harms or withdrawal outcomes were mixed.

Aripiprazole Plus Mood Stabilizers

Table 8 summarizes the bipolar type and major inclusion and exclusion criteria for each aripiprazole plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 8. Population and inclusion criteria for aripiprazole plus mood stabilizers studies for acute mania

Author, Year Single/Multisite Location Risk of Bias (ROB) PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
NCT00665366 2013 Multisite 3 Continents RoB NA	I: Aripiprazole + lithium/ valproate C: Placebo + lithium/ valproate	BD-I; DSM NR	Mean Age 45 (19-71) 54% Female 95% White N = 370	Mania/Manic/Mixed episode; YMRS ≥16	Schizoaffective Substance Abuse Other Mental Health Neurological disorders Pregnant/Nursing Labs/Other Conditions
Jeong, 201251 Multisite South Korea Low ROB 22592508	I: Aripiprazole + valproic acid C: Haloperidol + valproic acid	BD-I; DSM-IV	Mean Age 37 (NR) 64% Female Race NR N = 42	Mania; YMRS ≥20	Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions
Vieta, 200852 Multisite NR Moderate ROB 18381903	I: Aripiprazole + lithium/ divalproex/ valproate C: Placebo + lithium/ divalproex/ valproate	BD-I; DSM-IV	Mean Age 42 (18-78) 52% Female 92% White N = 384	Manic/Mixed episode; Partial responders to Lithium or Valproate; YMRS ≥ 16 with decrease of 25% between states	Substance Abuse Other Mental Health

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Aripiprazole Combination Versus Placebo

Evidence was insufficient for all outcomes from two RCTs (n=752), one published and one unpublished, to address whether aripiprazole with a mood stabilizer (e.g., lithium, valproic acid, or divalproex) was better than placebo for acute mania in adults with BD-I, due to high study limitations, inconsistency, and imprecise data.⁵² Results were mixed, with the published study reporting aripiprazole plus mood stabilizers showed improvements in response, remission, mania symptoms, and CGI, while the unpublished study reported no difference between groups. Both studies reported no differences between groups in withdrawal rates, serious adverse events, or rates of akathisia.

Aripiprazole Combination Versus Active Control

Evidence was insufficient for all outcomes from one small RCT (n=42) to address whether aripiprazole with mood stabilizers was better than haloperidol with mood stabilizer for acute mania in adults with BD-I, due to high study limitations, unknown consistency, and imprecise data.⁵¹ The study reported response rates in the 70 to 90 percent range but no differences between groups for mania symptom (YMRS) or CGI. Participants using aripiprazole reported experiencing more weight gain while participants using haloperidol reported experiencing more extrapyramidal symptoms.

Asenapine

We identified three eligible publications reporting three unique RCTs of asenapine and one RCT examining asenapine with lithium or valproic acid for acute mania with at least 3 weeks followup.^{25-27 59} Two studies were assessed as low to moderate risk of bias^{27 59} and two were assessed as high.^{25, 26} No additional studies were excluded for greater than 50 percent attrition. All were funded by industry. All interventions used a placebo comparator and two also compared to olanzapine.^{25, 26} Sample sizes ranged from 324 to 489 and all followed participants with BD-I.

Asenapine Alone

Table 9 summarizes the bipolar type and major inclusion and exclusion criteria for each study of asenapine alone for acute mania. [Appendix E](#) provides further detail.

Table 9. Population and inclusion criteria for studies of asenapine alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Landbloom, 2016 ²⁷ Multisite 3 Continents Low ROB 26496015	I: Asenapine C: Placebo	BD-I; DSM-IV	Mean Age 44 (18-77) 55% Female Race NR N = 367	Mania; Structured clinical interview (MINI). Episode began at least 1 month prior to screening. YMRS ≥ 20	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions
McIntyre, 2010 ²⁵ Multisite 3 Continents High ROB 20096936	I: Asenapine C1: Placebo C2: Olanzapine	BD-I; DSM-IV	Mean Age 39 (18-74) 47% Female 55% White N = 488	Manic/Mixed; YMRS ≥ 20; Current episode ≤ 3 months	First Manic Episode Neurological Disorders Substance Abuse Other Mental Health Taking Other Meds Lab/Other Conditions
McIntyre, 2009 ²⁶ Multisite 3 continents High ROB 19839993	I: Asenapine C1: Placebo C2: Olanzapine	BD-I; DSM-IV	Mean Age 39 (18-74) 43% Female 61% White N = 488	Manic/Mixed; YMRS ≥ 20; Current episode ≤ 3 months	First Manic Episode Neurological Disorders Substance Abuse Taking Other Meds Labs/Other Conditions

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Asenapine Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from three studies (n=956) showed asenapine improved mania symptoms (YMRS mean difference 4.37, 95% CI 1.27, 7.47) and CGI (mean difference 0.5, 95% CI 0.29, 0.71) compared to placebo after 3 weeks of treatment, although the improvement was about two-thirds the MID.²⁵⁻²⁷ Response and remission were not significantly different between groups. We found low-strength evidence that asenapine had a lower rate of withdrawal due to lack of efficacy than placebo (moderate study limitations, imprecision). However, low-strength evidence also showed that placebo had a lower rate of withdrawal due to adverse events than asenapine (moderate study limitations, imprecision). Overall withdrawal was less in the asenapine group, and favored asenapine over placebo, but results were not statistically significant. There were no differences between groups for serious adverse events, although participants with asenapine had significantly more extrapyramidal symptoms than those on placebo.

Asenapine Alone Versus Active Control

Evidence was insufficient for all outcomes from two studies (n=763) to address whether asenapine was better than olanzapine for acute mania in adults with BD-I, due to high study limitations and imprecise data.^{25, 26} Studies reported olanzapine showed a greater response rate but no differences in remissions. Serious adverse events were not different between arms, although participants using asenapine tended to withdraw at higher rates.

Asenapine Plus Mood Stabilizers

Table 10 summarizes the bipolar type and major inclusion and exclusion criteria for each asenapine plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 10. Population and inclusion criteria for asenapine plus mood stabilizer studies for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Szegedi, 2012 ⁵⁹ Multisite 4 Continents Moderate ROB 22198448	I: Asenapine + lithium/ valproate C: Placebo + lithium/ valproate	BD-I; NR	Mean Age 39 (18-75) 43% Female 57% White N = 324	Mania; YMRS ≥ 20 Current episode ≤3 months	Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions First Manic Episode

BD=Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Asenapine Combination Versus Placebo

Evidence from this single study of 324 participants with BD-I was rated as insufficient for all outcomes due to moderate study limitations, unknown consistency, and imprecision. The study reported the asenapine with lithium or valproate group showed improvement in manic symptom (YMRS) and CGI but no differences between groups for response or remission rates.

Cariprazine

We identified three eligible publications reporting three unique RCTs of cariprazine for acute mania with at least 3 weeks followup.²⁸⁻³⁰ All were assessed as low to moderate risk of bias and used a placebo comparator. No studies were excluded for greater than 50 percent attrition. All were funded by industry. Sample sizes ranged from 238 to 497 and all recruited participants with BD-I. Table 11 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix E](#) provides further detail.

Table 11. Population and inclusion criteria for studies of cariprazine alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Calabrese, 2015 ²⁸ Multisite 3 Continents Low ROB 25562205	I: Cariprazine C: Placebo	BD-I; DSM-IV	Mean Age 42 (18-65) 47% Female 69% White N = 497	Manic/Mixed; YMRS ≥ 20 AND ≥ 4 on two YMRS items AND MADRS <18	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Durgam, 2015 ²⁹ Multisite 3 Continents Moderate ROB 25056368	I: Cariprazine C: Placebo	BD-I; DSM-IV	Mean Age 38 (18-65) 67% Female 43% White N = 306	Manic/Mixed; YMRS ≥ 20 AND ≥ 4 on two YMRS items	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions
Sachs, 2015 ³⁰ Multisite 2 Continents Moderate ROB 25532076	I: Cariprazine C: Placebo	BD-I; DSM-IV	Mean Age 36 (18-65) 36% Female 21% White N = 312	Manic/Mixed; YMRS ≥ 20 YMRS AND ≥ 4 on two YMRS items AND MADRS <18	Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Cariprazine Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from three studies (n=1,047) showed cariprazine improved response (OR 2.14, 95% CI 1.08, 4.23) and remission (OR 1.95, 95% CI 1.45, 2.63) rates, as well as mania symptoms (YMRS mean difference 5.38, 95% CI 1.84, 8.92) and CGI-BP-S (mean difference 0.54, 95% CI 0.35, 0.73), compared to placebo after 3 weeks of treatment.²⁸⁻³⁰ No differences were seen in withdrawal rates. There were no differences between groups for serious adverse events, although participants using cariprazine had more extrapyramidal symptoms than those using placebo.

Olanzapine

We identified 15 eligible publications reporting 13 unique RCTs of olanzapine and seven eligible publications reporting five unique RCTs of olanzapine with a mood stabilizer for acute mania with at least 3 weeks followup.^{25, 26, 31, 33, 34, 44-46, 60-72} Five were assessed as low risk of bias, five as moderate, and eight as high. Fourteen studies reported being funded by industry. An additional sixteen studies were excluded for greater than 50 percent attrition.⁷³⁻⁸⁸ Nine studies used a placebo comparator, while 14 used active comparators. Two studies of olanzapine with mood stabilizers did not use a placebo in place of olanzapine.^{46, 69} Sample sizes ranged from 30 to 560 and most reported recruiting participants with BD-I; one study restricted participants to a current DSM-IV mixed episode.⁶⁹

Olanzapine Alone

Table 12 summarizes the bipolar type and major inclusion and exclusion criteria for each study of olanzapine alone for acute mania. [Appendix E](#) provides further detail.

Table 12. Population and inclusion criteria for studies of olanzapine alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Xu, 2015 ⁴⁶ Singlesite China Low ROB 26060401	I: Olanzapine C1: Olanzapine + Valproate C2: Valproate	BD-I; DSM-IV	Mean Age 31 (19-60) 52% Female Race NR N = 120	Manic; YMRS ≥ 17	Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing
Katagiri, 2012 ³¹ Multisite Japan Moderate ROB 22134043	I: Olanzapine C1: Placebo (Haloperidol arm excluded for <10 completers)	BD-I; DSM-IV	Mean Age 43 (21-65) 55% Female Race NR N = 221	Manic or Mixed Episode; YMRS ≥ 20	Other Mental Health Taking Other Meds Labs/Other Conditions
McIntyre, 2010 ³² Multisite 3 Continents High ROB 20096936	I: Olanzapine C1: Placebo C2: Asenapine	BD-I; DSM-IV	Mean Age 39 (18-61) 47% Female 55% White N = 488	Manic or Mixed Episode; YMRS ≥ 20	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions
Shafti, 2010 ⁶⁴ Singlesite Iran Moderate ROB 19740546	I: Olanzapine C: Lithium	BD-I; DSM-IV	Mean Age NR 100% Female Race NR N = 40	Manic (particulars not described)	Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Labs/Other Conditions
McIntyre, 2009 ²⁶ Multisite 3 Continents High ROB 19839993	I: Olanzapine C1: Placebo C2: Asenapine	BD-I; DSM-IV	Mean Age 40 (18-74) 43% Female 61% White N = 489	Manic or Mixed Episode; YMRS ≥ 20	Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions
Niufan, 2008 ⁶¹ Multisite China Low ROB 17531327	I: Olanzapine C: Lithium	BD-I; DSM-IV	Mean Age 33 (18-72) 74% Female Race NR N = 140	Manic or Mixed Episode; YMRS ≥ 20	NR
Tohen, 2008b ³³ Multisite 3 Continents Low ROB 19014751	I: Olanzapine C1: Placebo C2: Divalproex	BD-I; DSM-IV	Mean Age 40 (18-65) 60% Female Race NR N = 521	Manic or Mixed Episode without psychotic features; YMRS 20-30 CGI-BP mania 3- 4	Schizoaffective Other Mental Health Pregnant/Nursing

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Perlis, 2006 ⁸⁹ Multisite US High ROB 17196055	I: Olanzapine C: Risperidone	BD-I; DSM-IV	Mean Age 38 (18-70) 55% Female 74% White N = 329	Manic; YMRS \geq 20	Substance Abuse Labs/Other Conditions
Zajacka, 2002 ⁴⁵ Multisite US Moderate ROB 12523875 12716270 ⁶³	I: Olanzapine C: Divalproex	BD-I; DSM-IV	N = 120 Age 39 (18-65) 46% Female 75% White	Mania; SADS-C \geq 25 with at least four scale items rated at least 3.	Schizoaffective; Substance Abuse; Other Mental Health Conditions; Neurological Disorders; Taking other medications; Pregnant/Nursing; Labs/Other conditions
Tohen, 2003 ⁶⁷ Multisite 4 Continents Moderate ROB 14662554 12177585 ⁶⁵	I: Olanzapine C: Haloperidol	BD-I; DSM-IV	Mean Age 40 (18-80) 60% Female Race NR N = 453	Manic; YMRS \geq 20	Substance Abuse Labs/Other Conditions
Tohen, 2002b ⁴⁴ Multisite US High ROB 12042191	I: Olanzapine C: Divalproex	BD-I; DSM-IV	Mean Age 41 (18-75) 57% Female 81% White N = 251	Mania; YMRS \geq 20	Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions
Tohen, 2000 ³⁴ Multisite US High ROB 10986547	I: Olanzapine C: Placebo	BD-I; DSM-IV	Mean Age 39 (18-69) 50% Female 80% White N = 115	Mixed Episode; YMRS score \geq 20	Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Meds; Labs/Other Conditions
Berk, 1999 ⁶⁰ Singlensite South Africa High ROB 10565800	I: Olanzapine C: Lithium	NR; DSM-IV	Mean Age 31 (NR) Sex NR Race NR N = 30	Mania No criteria specific reported	Other Mental Health; Pregnant/Nursing; Labs/Other Conditions

BD=bipolar disorder; C=Comparison; CGI-BP-S=Clinical global impression scale, bipolar edition, severity; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS= Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; SADS-C=Schedule for Affective Disorders and Schizophrenia, change version; YMRS=Young Mania Rating Scale

Olanzapine Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from five RCTs (n=1,199) showed olanzapine was better for acute mania than placebo in response (OR 1.99, 95% CI 1.29 to 3.08) and remission (OR 1.75, 95% CI 1.19 to 2.58) rates. Mania symptom improvement was close to a MID (YMRS, mean difference 4.9, 95% CI 2.34 to 7.45).^{25, 26, 31, 33, 34, 45} CGI trended

toward improvement for olanzapine but did not reach significance. Low-strength evidence (moderate study limitations, imprecision) also showed overall withdrawal and withdrawal due to lack of effect were lower for olanzapine. Withdrawal for adverse events did not differ between groups. While serious adverse events did not differ by group, participants using olanzapine reported more extrapyramidal symptoms and weight gain (at least 7 percent increase) than those using placebo.

Olanzapine Alone Versus Active Control

Low-strength evidence (moderate study limitations, imprecision) from four RCTs (n=867) showed no statistically significant difference in outcomes between olanzapine versus divalproex or valproate for acute mania in adults with presumed BD-I.^{33, 44-46, 63, 66} No differences were noted in response or remission rates (n=635), mania symptoms (YMRS, n=750), CGI (n=578), or withdrawals (n=867). No differences were noted in serious adverse events. However, one study noted participants receiving olanzapine experienced more clinically important weight gain (at least 7%) than those receiving divalproex;³³ a trend toward greater weight gain in olanzapine groups was noted in the other studies as well.

Evidence was insufficient for all outcomes from three RCTs (n=210) to address whether olanzapine was better for acute mania than lithium in adults with presumed BD-I, due to moderate study limitations, inconsistency, and imprecision.^{60, 61, 64} The studies reported mixed results for response, mania symptom improvement (YMRS), or CGI. Withdrawals and adverse events tended to show no differences between groups.

Evidence was also insufficient for all outcomes to address whether olanzapine was better than risperidone (one RCT, n=329),⁸⁹ or haloperidol (one RCT, n=453), due to single studies of moderate to high study limitations and imprecision.⁶⁷ The studies reported no differences between groups for response, remission, symptom improvement, function, or withdrawals over 3 weeks. No differences between groups were noted in serious adverse events. However, participants using olanzapine reported more weight gain while participants using haloperidol reported more akathisia.

Results for olanzapine versus asenapine were reported in the asenapine versus active comparator section above (e.g., evidence was insufficient for olanzapine compared to asenapine).

Olanzapine Plus Mood Stabilizers

Table 13 summarizes bipolar type and major inclusion and exclusion criteria for each olanzapine plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 13. Population and inclusion criteria for olanzapine plus mood stabilizers studies for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Conus, 2015 ⁶⁸ Singlesite Australia Low ROB 26485297	I: Olanzapine + Lithium C: Chlorpromazine + Lithium	BD-I; DSM-IV	Mean Age 22 (15-28) 32% Female Race NR N = 83	Manic or Mixed Episode; YMRS ≥ 20	Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Xu, 2015 ⁴⁶ Singlesite China Low ROB 26060401	I: Olanzapine + Valproate C1: No placebo + Olanzapine C2: No placebo + Valproate	BD-I; DSM-IV	Mean Age 31 (19-60) 52% Female Race NR N = 114	Manic; YMRS ≥ 17	Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing
Houston, 2009 ⁶⁹ Multisite US and Puerto Rico High ROB 19778495	I: Olanzapine + Divalproex C: Placebo +Divalproex	BD-I; DSM-IV	Mean Age 39 (18-60) 59% Female 51% White N = 202	Mixed Episode; YMRS ≥ 16 HDRS-21 (inadequate response to divalproex)	First Manic Episode Taking Other Meds Labs/Other Conditions
Tohen, 2008a ⁷⁰ Multisite 3 Continents Moderate ROB 18245032	I: Olanzapine + Carbamazepine C: Placebo + Carbamazepine	BD-I; DSM-IV	Mean Age 41 (18-65) 60% Female Race NR N = 118	Manic or Mixed Episode; YMRS ≥ 20	Labs/Other Conditions
Tohen, 2002a ⁶⁶ Multisite US and Canada High ROB 11779284 15337326 ⁷¹ 15572737 ⁷²	I: Olanzapine + Lithium of Valproate C: Placebo + Lithium or Valproate	BD-I; DSM-IV	Mean Age 41 (18-70) 52% Female 85% White N = 344	Manic or Mixed Episode; YMRS ≥ 16 (partially nonresponsive to lithium or valproate)	First Manic Episode Labs/Other Conditions

BD=Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Olanzapine Combination Versus Placebo/No Placebo

Evidence was insufficient for all outcomes from four RCTs to address whether olanzapine plus mood stabilizers was better for acute mania than mood stabilizers alone for adults with BD-I, due to high study limitations and imprecision. Two studies examined olanzapine plus carbamazepine (n=118)⁷⁰ or lithium/valproate (n=344).⁶⁶ The studies showed mixed results for response or remission rates, but both reported olanzapine improved symptoms. Two other studies examined olanzapine plus divalproex (n=202)⁶⁹ or valproate (n=80)⁴⁶ compared to the mood stabilizer alone without a placebo present. One study reporting response and remission rates reported results favoring olanzapine, while both reported improvements in mania symptoms. Participants receiving olanzapine reported greater frequency of clinically important weight gain. No other differences between groups were noted in serious adverse events.

Olanzapine Combination Versus Active Control

Evidence was insufficient for all outcomes from one RCT (n=83) to address whether olanzapine plus lithium was better for acute mania than chlorpromazine plus lithium for adults with BD-I, due to a single study and imprecision.⁶⁸ The study reported no difference between groups for all outcomes including symptomatic recovery, response, remission, depressive symptoms, and CGI. No differences were noted in serious adverse events or clinically significant weight gain.

Quetiapine

We identified six eligible publications reporting six unique RCTs of quetiapine and two eligible publications reporting two unique RCTs of quetiapine plus mood stabilizers for acute mania with at least 3 weeks followup.^{35-39, 90-92} Two studies were assessed as low risk of bias, three as moderate, and three as high risk. Three additional studies were excluded for greater than 50 percent attrition.^{93, 94, 95} All studies were funded by industry. Five studies used placebos and three used active comparators. Sample sizes ranged from 39 to 493. All enrolled participants with BD-I; one study restricted participants to a current episode of mania but a history of manic or mixed episodes in the last 5 years. Another small study enrolled participants with mild to moderate hypomania or mild mania regardless of type of BD.³⁹

Quetiapine Alone

Table 14 summarizes the bipolar type and major inclusion and exclusion criteria for each study of quetiapine alone for acute mania. [Appendix E](#) provides further detail.

Table 14. Population and inclusion criteria for studies of quetiapine alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Cutler, 2011 ³⁸ Multisite US Low ROB 22054797	I: Quetiapine ER C: Placebo	BD-I; DSM-IV	Mean Age 41 (18-65) 40% Female 47% White N = 308	Mania; YMRS ≥ 20 overall; YMRS ≥ 4 on at least 2 of 4 specified mania domains, and CGI-BD-S ≥ 4	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Labs/Other Conditions
McElroy, 2010 ³⁹ Singlensite US Moderate ROB 19963274	I: Quetiapine C: Placebo	BD-I, II, NOS; DSM-IV	Mean Age 35 (18-75) 51% Female 69% White 74% BD-I 21% BD-II 5% BD-NOS N = 41	Mild to moderate hypomania or mild mania; CGI-BD ≥ 3 AND <5	Substance Abuse Other Mental Health Neurological Disorders Pregnant Nursing Labs/Other Conditions
Vieta, 2010 ³⁵ Multisite 3 continents High ROB 20565430	I: Quetiapine C: Placebo (Paliperidone arm comparisons in Other Drugs section)	BD-I; DSM-IV	Mean Age 39 (18-65) 43% Female Race NR N = 493	Mania; YMRS ≥ 20	First Manic Episode Schizoaffective Substance Abuse Neurological Disorders
Li, 2008 ⁹⁰ Multisite China Moderate ROB 18028587	I: Quetiapine C: Lithium	BD-I; CCMD-3	Mean Age 33 (18-65) 53% Female Race NR N = 155	Mania; YMRS ≥ 20	Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Bowden, 2005 ³⁶ Multisite 2 Continents High ROB 15669897	I: Quetiapine C1: Lithium C2: Placebo	BD-I; DSM-IV	Mean Age 39 (18-73) 42% Female Race NR N = 300	Mania; YMRS \geq 20 including score of at least 4 on 2 of the 4 double-weighted items (irritability, speech, content, and disruptive/aggressive behavior), CGI \geq 4	First Manic Episode Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions
McIntyre, 2005 ³⁷ Multisite 3 Continents Moderate ROB 16139175	I: Quetiapine C1: Haloperidol C2: Placebo	BD-I; DSM-IV	Mean Age 43 (18-79) 63% Female Race NR N = 299	Mania; YMRS \geq 20 AND \geq 4 on at least 2 YMRS subscales AND \geq 4 on CGI-BD-S	First Manic Episode Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions

BD=bipolar disorder; C=Comparison; CCMD= Chinese Classification and Diagnosis Criteria of Mental Disorder, 3rd Version ; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; CGI=Clinical global impression scale, bipolar edition, severity; I=Intervention; MADRS= Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Quetiapine Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from four RCTs showed improved response rates (OR 2.07, 95% CI 1.39 to 3.09, n=1,007) and manic symptom improvement close to the MID (YMRS, mean difference 4.92, 95% CI 0.31 to 9.53, n=699) for participants receiving quetiapine.³⁵⁻³⁸ Evidence was insufficient to address remission rates (n=699) due to fewer studies of higher risk of bias contributing to the outcome. Low-strength evidence (moderate study limitations, imprecision) showed CGI improved for participants using quetiapine, but the improvement was about half the MID (mean difference 0.54, 95% CI 0.35 to 0.74, n=806). Withdrawal due to lack of efficacy was lower for quetiapine but overall withdrawal and withdrawal due to adverse events did not differ between groups (low-strength, n=1,007). Most studies reported no serious adverse events and no differences between groups for extrapyramidal symptoms. One small study (n=41) enrolling patients with mild to moderate hypomania or mild mania also found participants using quetiapine showed improvements in manic symptoms (YMRS) and CGI.³⁹ Weight gain greater than 7 percent was infrequently reported but tended to be more common in participants using quetiapine.

Quetiapine Alone Versus Active Control

Evidence was insufficient for all outcomes from one RCT (n=199) to address whether quetiapine was better for acute mania than haloperidol in adults with BD-I, due to a single study and imprecision.³⁷ The study reported no differences between groups for response or remission rates, manic symptom improvement, CGI, or withdrawals. Participants using haloperidol reported more extrapyramidal symptoms; otherwise, no differences in serious adverse events were noted.

Evidence was insufficient from two RCTs (n=456) to address whether quetiapine was better for acute mania than lithium for in adults with BD-I, due to high study limitations, inconsistency, and imprecision.^{36, 90} Both studies reported response and remission rates, and change in manic symptoms; one trial reported benefit with quetiapine⁹⁰ and one reported no difference.³⁶ One trial reported no difference in CGI.³⁶ Both reported no difference in withdrawals or serious adverse events.

Quetiapine Plus Mood Stabilizers

Table 15 summarizes bipolar type and major inclusion and exclusion criteria for each quetiapine plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 15. Population and inclusion criteria for quetiapine plus mood stabilizer studies for acute mania

Author, Year Single- Multisite Local/ Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Yatham, 2007 ⁹¹ Multisite 4 Continents High ROB 17519644	I: Quetiapine + Lithium/ Valproate C: Placebo + Lithium/ Valproate	BD-I; DSM-IV	Mean Age 40 (range NR) 50% Female Race NR N = 200	Mania; YMRS ≥ 20 AND ≥ 4 on at least 2 YMRS subscales AND CGI- BP-S ≥ 4	First Manic Episode Taking Other Meds Pregnant/Nursing
Yatham, 2004 ⁹² Singlesite 4 continents Moderate ROB 15538120	I: Quetiapine + Lithium/ Valproate C: Placebo + Lithium/ Valproate	BD-I; DSM-IV	Mean Age NR (18-70) 47% Female Race NR N = 370	Mania; At least one manic or mixed episode in previous 5 years. YMRS≥20, including score ≥4 on two core YMRS items; CGI- BP≥4	First Manic Episode Substance Abuse Other Mental Health Pregnant/Nursing

BD=Bipolar Disorder; C=Comparison; CGI-BP-S=Clinical Global Impression scale, bipolar edition, severity; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Quetiapine Combination Versus Placebo

Evidence was insufficient for all outcomes from two RCTs (n=570) to address whether quetiapine plus mood stabilizers was better for acute mania than mood stabilizer alone in adults with BD-I, due to high study limitations and imprecise data.^{91, 92} The studies reported quetiapine added to mood stabilizers improved response and remission rates, manic symptoms (YMRS), and CGI score. Both studies reported no differences between groups in withdrawal rates and serious adverse events, and results for extrapyramidal symptoms were mixed.

Risperidone

We identified three eligible publications reporting three unique RCTs of risperidone and one RCT for risperidone plus mood stabilizers for acute mania with at least 3 weeks followup.^{40, 41, 96} One study was assessed as low risk of bias and three studies were assessed as moderate. All

were funded by industry. Four additional studies were excluded for greater than 50 percent attrition.^{84, 94, 98, 99} Three studies used placebo comparators and two studies used active comparators. Sample sizes ranged from 45 to 438 and enrolled BD-I participants.

Risperidone Alone

Table 16 summarizes the bipolar type and major inclusion and exclusion criteria for each study of risperidone alone for acute mania. [Appendix E](#) provides further detail.

Table 16. Population and inclusion criteria for studies of risperidone alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Khanna, 2005 ⁴⁰ Multisite India Moderate ROB 16135859	I: Risperidone C:Placebo	BD-I; DSM-IV	Mean Age 35 (NR) 38% Female Race NR N = 290	Mania; YMRS ≥ 20	Schizoaffective Substance Abuse Other Mental Health Taking Other Meds
Smulevich, 2005 ⁴¹ Multisite 2 Continents Moderate ROB 15572276	I: Risperidone C1: Haloperidol C2: Placebo	BD-I; DSM-IV	Mean Age 40 (18-79) 49% Female Race NR N = 438	Mania; YMRS ≥ 20 and MADRS ≤ 20	First Manic Episode Schizoaffective Substance Abuse Other Mental Health Taking Other Meds
Segal, 1998 ⁹⁶ Singlesite South Africa Moderate ROB 9617509	I: Risperidone C1: Haloperidol C2: Lithium	BD-I, DSM-IV	Mean Age 34 (19-58) 78% Female Race NR N = 45	Manic; DSM-IV Criteria for bipolar disorder, manic phase	Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Risperidone Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from two studies (n=584) showed risperidone was better for acute mania than placebo for adults with BD-I.^{40, 41} Although we were unable to conduct a meta-analysis based on the two studies, the finding in favor of risperidone was consistent across the studies for response rate, manic symptom improvement (YMRS), and CGI. No serious adverse events were reported. However, participants using risperidone experienced more extrapyramidal symptoms than those using placebo.

Risperidone Alone Versus Active Control

Evidence was insufficient for all outcomes to address whether risperidone performed better than an active comparator for acute mania, due to moderate study limitations, inconsistency, and imprecision. Findings were mixed from two studies comparing risperidone to haloperidol in adults with BD-I.^{41, 96} Those who received risperidone also had lower total scores on the extrapyramidal symptom rating scale at 3 weeks compared to those who received haloperidol.

Withdrawal rates were similar between groups. One study compared risperidone to lithium, finding no difference between groups in bipolar outcomes and extrapyramidal symptoms at 4 weeks.⁹⁶ Withdrawal rates were not reported.

Results for risperidone versus olanzapine were reported in the olanzapine versus active comparator section above and were determined to yield insufficient evidence.

Risperidone Plus Mood Stabilizers

Table 17 summarizes bipolar type and major inclusion and exclusion criteria for each risperidone plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 17. Population and inclusion criteria for risperidone plus mood stabilizer studies for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Yatham, 2003 ⁹⁷ Multisite 4 Continents Low ROB 12562742	I: Risperidone + Lithium or Divalproex or Carbamazepine C: Placebo + Lithium or Divalproex or Carbamazepine	BD-I; DSM-IV	Mean Age NR (19-65) 58% Female Race NR N = 150	Mania; YMRS ≥ 20	Schizoaffective Substance Abuse Other Mental Health Pregnant/Nursing Labs/Other Conditions

BD=Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Risperidone Combination Versus Placebo

Evidence from this single study of 150 participants with BD-I was rated as insufficient due to unknown consistency and imprecision. The study reported that adding risperidone to mood stabilizers improved response rates and CGI and a trend toward reduced manic symptoms (YMRS). No differences were reported in adverse events; however, participants using risperidone experienced more extrapyramidal symptoms.

Ziprasidone

We identified two eligible publications reporting two unique RCTs of ziprasidone and one RCT of ziprasidone plus mood stabilizers for acute mania with at least 3 weeks followup.^{42, 43, 100} Two studies were assessed as moderate risk of bias, and one was high. All were funded by industry. Two additional studies were excluded for greater than 50 percent attrition.^{101, 102} Sample sizes ranged from 197 to 680.

Ziprasidone Alone

Table 18 summarizes the bipolar type and major inclusion and exclusion criteria for each study of ziprasidone alone for acute mania. [Appendix E](#) provides further detail.

Table 18. Population and inclusion criteria for studies of ziprasidone alone for acute mania

Author, Year Single- Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Potkin, 2005 ⁴² RCT Multisite 2 Continents Moderate ROB 16012271	I: Ziprasidone C: Placebo	BD-I; DSM-IV	Mean Age 39 (19-71) 49% Female 62% White N = 205	Mania; YMRS \geq 14 with score \geq 2 on four items at screening and admission	Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Pregnant/Nursing
Keck, 2003 ⁴³ RCT Multisite 2 Continents Moderate ROB 12668364	I: Ziprasidone C: Placebo	BD-I; DSM-IV	Mean Age 38 (18-66) 46% Female Race NR N = 197	Current Manic episode; YMRS \geq 14 with score \geq 2 on four items at screening and admission	Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Pregnant/Nursing Labs/Other Conditions

BD=bipolar disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Ziprasidone Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from two studies (n=402) showed ziprasidone was better for acute mania than placebo in adults with BD-I.^{42, 43} Although we were unable to conduct a meta-analysis, the finding in favor of ziprasidone was consistent across the studies for response rate, manic symptom improvement (YMRS), and CGI. Withdrawal due to lack of effect also was lower for the ziprasidone group, while no differences were seen for overall withdrawal or adverse events. Serious adverse events were reported in one study, with no difference between groups. However, in one study participants using ziprasidone experienced more extrapyramidal symptoms than those using placebo.⁴²

Ziprasidone Plus Mood Stabilizers

Table 19 summarizes bipolar type and major inclusion and exclusion criteria for each ziprasidone plus mood stabilizers study for acute mania. [Appendix E](#) provides further detail.

Table 19. Population and inclusion criteria for ziprasidone plus mood stabilizer studies for acute mania

Author, Year Single-Multisite Local/Contin ent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Sachs, 2012 ¹⁰⁰ RCT Multisite US High ROB 23218157	I1: Low Dose Ziprasidone 40-80 mg/day + Lithium/Valproate I2: High Dose Ziprasidone 120-160 mg/day + Lithium/Valproate C: Placebo + Lithium/Valproate	BD-I; DSM-IV	Mean Age 41 (NR) 50% Female 65% White N = 680	Mania; YMRS ≥ 18 with 25% improvement between screening and baseline; current episode ≤ 3 months	First manic episode Schizoaffective Substance Abuse Other Mental Health Conditions Taking Other Meds Labs/Other Conditions

BD=Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Ziprasidone Combination Versus Placebo

Evidence from a single study of 680 participants with BD-I was rated as insufficient due to a single high risk of bias study and imprecision. The study reported no differences between groups in manic symptom (YMRS) and CGI. No differences were reported in adverse events, however participants using high dose ziprasidone experienced more extrapyramidal symptoms.

Haloperidol

We identified two eligible publications reporting two unique RCTs of haloperidol for acute mania with at least 3 weeks followup.^{37, 41} One study was assessed as moderate risk of bias⁴¹ and one was assessed as high.³⁷ Both were funded by industry. One additional study was excluded for greater than 50 percent attrition.⁷³ Both studies used a placebo comparator. Sample sizes ranged from 299 to 438 and recruited participants with BD-I.

Haloperidol Alone

Table 20 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix E](#) provides further detail.

Table 20. Population and inclusion criteria for studies of haloperidol alone for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
McIntyre, 2005 ³⁷ Multisite 3 Continents Moderate High ROB (for haloperidol comparisons) 16139175	I: Haloperidol C1: Quetiapine C2: Placebo	BD-I; DSM-IV	Mean Age 43 (18-79) 63% Female Race NR N = 299	Manic; YMRS \geq 20 CGI-BP \geq 4	First Manic Episode Substance Abuse Other Mental Health Neurological disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions
Smulevich, 2005 ⁴¹ Multisite NR Moderate ROB 15572276	I: Haloperidol C1: Risperidone C2: Placebo	BD-I; DSM-IV	Mean Age 40 (18-83) 47% Female 65% White N = 438	Manic YMRS \geq 20 AND MADRS \leq 20	Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions

BD=Bipolar Disorder; C=Comparison; CGI-BP= clinical global impression scale, bipolar edition; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS=Montgomery-Asberg depression scale; N=number; NR=Not Reported; ROB=Risk of Bias; YMRS=Young Mania Rating Scale

Haloperidol Versus Placebo

Evidence was insufficient for all outcomes from two studies (n=483) to address whether haloperidol was better for acute mania than placebo in participants with BD-I, due to high study limitations and imprecision.^{37, 41} Studies reported results generally favored haloperidol. Neither study reported serious adverse events.

Haloperidol Versus Active Control

Results for haloperidol versus aripiprazole were reported in the aripiprazole versus active comparator section above and yielded insufficient evidence.

Mood Stabilizers for Acute Mania

Key Points

- Studies for mood stabilizers were sparse and scattered.
- Evidence was largely insufficient to draw conclusions regarding mood stabilizers compared to placebo or other drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).
- Low-strength evidence showed lithium increased response and remission rates and manic symptom improvement in BD-I participants with acute mania compared to placebo.
- When reported, all comparisons tended to show no differences between groups in serious adverse events. Participants using carbamazepine reported experiencing more severe rash and adverse events compared to placebo.
- The ability to draw stronger conclusions was hindered by high attrition rates.

Eligible Studies for Mood Stabilizers

Four mood stabilizers, all FDA approved for use in patients with bipolar disorder experiencing mania, were examined in 12 publications of 12 unique studies for BD patients with acute mania. All were tested as single drugs: carbamazepine, divalproex/valproate, lamotrigine, and lithium. All studies enrolled adults with BD-I. Only one study (for lithium) also included adults with BD-II. There were no studies assessing drug effectiveness in treatment of hypomania. The large majority of studies with usable outcomes were measured at 3 weeks duration.

[Appendix F](#) provides detailed evidence tables, summary risk of bias assessments, forest plots when appropriate, and assessments of strength of evidence for key comparisons and outcomes. A summary of findings with at least low-strength evidence for mood stabilizers for acute mania are provided in Table 21. Any intervention and comparison not listed in Table 21, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 21. Summary of findings with at least low-strength evidence for mood stabilizers for acute mania

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Lithium vs. placebo	1 RCT ³⁶ + 1 IPD ¹⁰³ (n=325) 3 weeks	Remission and Response Rates: Favors Lithium (not pooled)	Low (moderate study limitations, imprecise)
	3 RCTs ^{36, 103} (n=325) 3 weeks	YMRS: Favors Lithium, MD 5.81 (95% CI 2.21, 9.4; MID=6) Withdrawal (Overall): No difference	Low (moderate study limitations, imprecise)
	1 IPD ¹⁰³ (n=450) 3 weeks	Withdrawal (Lack of Efficacy, AE): No difference	Low (moderate study limitations, imprecise)

AE=adverse events; CI=confidence interval; IPD=Individual patient data; MD=mean difference; MID=minimally important difference; n=number; RCT=randomized controlled trial; YMRS=Young mania rating scale

Carbamazepine

We identified four RCTs examining carbamazepine for acute mania with at least 3 weeks followup.¹⁰⁴⁻¹⁰⁷ One study was moderate risk of bias and three were high. Three additional studies were excluded for greater than 50 percent attrition.¹⁰⁸⁻¹¹⁰ Three studies were funded at least in part by industry. One study used placebo¹⁰⁴ and three used active comparators.¹⁰⁵⁻¹⁰⁷ Sample sizes ranged from 30 to 443. All trials recruited participants with BD-I. Table 22 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix F](#) provides further detail.

Table 22. Population and inclusion criteria for carbamazepine for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Weisler, 2006 ¹⁰⁴ Multisite 2 Continents High ROB 16529527	I: Carbamazepine C: Placebo	BD-I; DSM-IV	Mean Age 38 (18-76) 38% Female 59% White N = 443	Manic/Mixed; YMRS ≥ 20	Taking Other Meds
Vasudev, 2000 ¹⁰⁵ Singlesite India Moderate ROB 10867972	I: Carbamazepine C: Valproate	BD-I; DSM-III	Mean Age NR 80% Female Race NR N = 30	Mania; DSM-III-R criteria for BD diagnosis; YMRS ≥ 20	Substance Abuse Neurological Disorders Taking other meds Pregnant/Nursing
Small, 1991 ¹⁰⁶ Singlesite US High ROB 1929761	I: Carbamazepine C: Lithium	BD-I; DSM-III	Mean Age 39 (22-73) 38% Female 59% White N = 48	Manic/Mixed; YMRS ≥ 20	First Manic Episode Substance Abuse Other Mental Health
Lerer, 1987 ¹⁰⁷ Singlesite US High ROB 3546274	I: Carbamazepine C: Lithium	BD-I; DSM-III	Mean Age 41 (23-65) 54% Female Race NR N = 34	Mania (not defined)	Neurological Disorders

BD =Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; =number;
NR=Not Reported; ROB=risk of bias; YMRS=Young Mania Rating Scale

Carbamazepine Alone Versus Placebo

Evidence was insufficient for all outcomes from one pooled analysis (n=443) of two high risk of bias trials to address whether carbamazepine was better for acute mania than placebo in adults with BD-I, due to high study limitations and imprecision.¹⁰⁴ The study reported improvements in participants receiving carbamazepine in response rate, manic symptoms (YMRS) and CGI. Withdrawal for lack of efficacy and adverse events was lower for carbamazepine, but not overall withdrawals. Participants using carbamazepine experienced more frequent severe rash.

Carbamazepine Alone Versus Active Control

Evidence was insufficient for all outcomes from two small RCTs (n=82) for carbamazepine compared to lithium^{106, 107} and one small RCT (n=30) for carbamazepine versus valproate for acute mania in adults with BD-I, due to high study limitations and imprecision.¹⁰⁵ When reported, the studies generally reported no differences between groups for response rates, manic symptoms, CGI, or withdrawal rates. Participants receiving carbamazepine reported more adverse events. Evidence was also insufficient from one small RCT (n=30) for carbamazepine compared to valproate due to single study and imprecision.

Divalproex/Valproate

We identified two RCTs examining divalproex for acute mania with at least 3 weeks followup.^{33, 111} One study was low risk of bias and one was high. Both studies were funded by

industry. Two additional studies were excluded for greater than 50 percent attrition.^{112, 113} Both studies used placebo and one used active comparators. Sample sizes ranged from 364 to 521. One small study examining valproate versus no placebo was also included.⁴⁶ Seven additional valproate studies were excluded for greater than 50 percent attrition.¹¹⁴⁻¹²⁰ Table 23 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix F](#) provides details.

Table 23. Population and inclusion criteria for divalproex/valproate for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Xu, 2015 ⁴⁶ Singlesite China Low ROB 26060401	I: Olanzapine C1: Olanzapine + Valproate C2: Valproate	BD-I; DSM-IV	Mean Age 31 (19-60) 52% Female Race NR N = 120	Manic; YMRS ≥ 17	Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing
Tohen, 2008b ³³ Multisite 3 Continents Low ROB 19014751	I: Divalproex C1: Olanzapine C2: Placebo	BD-I; DSM-IV	Mean Age 40 (18-65) 49% Female Race NR N = 521	Mania/Mixed; YMRS ≥ 20 and ≤ 30; CGI-BP-S mania subscore 3 or 4	Schizoaffective Other Mental Health Conditions Pregnant/Nursing
Bowden, 2006 ¹¹¹ Multisite US High ROB 17107240	I: Divalproex C: Placebo	BD-I; DSM-IV	Mean Age 38 (18-65) 43% Female 74% White N = 364	Mania; Mania Rating Scale (From SADS-C interview) had to be at least 18 with at least 4 item scores >1.	First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health Conditions; Taking other Medications;

BD=Bipolar Disorder; C=Comparison; CGI-BP-S=Clinical Global Impression scale, bipolar edition, severity; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=risk of bias; SADS-C=Schedule for Affective Disorders and Schizophrenia-Change version; YMRS=Young Mania Rating Scale

Divalproex Alone Versus Placebo

Evidence was insufficient for all outcomes from two RCTs (n=670) to address whether divalproex sodium was better for acute mania than placebo in adults with BD-I, due to moderate to high study limitations, inconsistency, and imprecision.^{33, 111} Results were mixed for response, remission, and symptoms at 3 weeks. Both studies reported no difference in CGI or function (Global Assessment Score (GAS)), withdrawal, or serious adverse events.

Evidence was also insufficient for all outcomes from one small study (n=79) whether valproate plus olanzapine was better for acute mania than olanzapine alone in adults with BD-I, due to single study and imprecision. The study reported improvement in manic symptoms (YMRS) and CGI.

Divalproex Alone Versus Active Control

Results for divalproex versus olanzapine were reported in the olanzapine versus active comparator subsection of the antipsychotic section above (e.g., low-strength evidence for no difference in remission or response rates, or improvements in manic symptoms or function).

Lamotrigine

We identified a single small, industry-funded, moderate risk of bias RCT examining lamotrigine for acute mania with at least 3 week followup.¹²¹ Seven additional studies were excluded for attrition over 50 percent.^{53, 114, 115, 122-125} Table 24 summarizes the bipolar type and major inclusion and exclusion criteria. [Appendix F](#) provides details.

Table 24. Population and inclusion criteria for lamotrigine for acute mania

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Ichim, 2000 ¹²¹ Singlesite South Africa Moderate ROB 10798820	I: Lamotrigine C: Lithium	BD-I; DSM-IV	Mean Age 33 (NR) 47% Female Race NR N = 30	Mania	Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions

BD=Bipolar Disorder; C=Comparison; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; N=number; NR=Not Reported; ROB=risk of bias

Lamotrigine Alone Versus Active Control

Evidence was insufficient for all outcomes to address whether lamotrigine was better for acute mania than lithium in adults with BD-I, due to single study and imprecision. The study reported no differences between group in bipolar symptoms or response. No serious adverse events were reported and withdrawal rates were similar between groups.

Lithium

We identified three RCTs^{36, 96, 126} and one meta-analysis that pooled individual patient data from four RCTs¹⁰³ examining lithium for acute mania with at least 3 weeks followup. One study was low risk of bias, two moderate, and one high. Five additional studies were excluded for greater than 50 percent attrition.^{53, 58, 117, 118, 127} All studies were funded by industry. Two studies used placebo and all used active comparators. Sample sizes ranged from 45 to 876. Table 25 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix F](#) provides detail.

Table 25. Population and inclusion criteria for lithium for acute mania

Author, Year Single/Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Bowden, 2010 ¹²⁶ RCT Multisite 2 Continents Moderate ROB 20101186	I: Lithium C: Valproate	BD-I; DSM-IV	Mean Age 39 (18-75) Female 59% Race NR N = 270	Mania; YMRS ≥ 18	First Manic Episode Substance Abuse Pregnant/Nursing Labs/Other Conditions Other Mental Health

Author, Year Single/Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Kushner, 2006 ¹⁰³ Multisite 4 Continents Low ROB 16411977	I: Lithium C1: Placebo C2: Topiramate	BD-I; DSM-IV	Mean Age 41 (18-82) 53% Female 77% White N = 876	Mania; YMRS ≥ 20	Schizoaffective; Substance Abuse; Other Mental Health Conditions; Taking Other Medications;
Bowden, 2005 ³⁶ Multisite 3 Continents High ROB 15669897	I: Lithium C1: Placebo C2: Quetiapine	BD-I; DSM-IV	Mean Age 39 (18-73) 42% Female Race NR N = 300	Mania; YMRS ≥ 20 including score of at least 4 on 2 of the 4 double- weighted items (irritability, speech, content, and disruptive/aggressive behavior); CGI ≥ 4	First manic episode; Substance Use; Taking other medications; Pregnant/Nursing; Labs/Other Conditions
Segal, 1998 ⁹⁶ Singlensite South Africa Moderate ROB 9617509	I: Lithium C1: Haloperidol C2: Risperidone	BD-I; DSM-IV	Mean Age 34 (19-58) 78% Female Race NR N = 45	Mania; DSM-IV criteria for Bipolar Manic Phase	Substance Abuse; Taking other Medications; Pregnant/Nursing; Abnormal Lab Results

BD=Bipolar Disorder; C=Comparison; CGI=Clinical Global Impression; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; I=Intervention; MADRS= Montgomery-Asberg depression rating scale; N=number; NR=Not Reported; ROB=risk of bias; YMRS=Young Mania Rating Scale

Lithium Alone Versus Placebo

Low-strength evidence (moderate study limitations, imprecision) from one RCT and one meta-analysis of independent data from 4 RCTs (n=847) showed lithium increased response and remission rates in BD-I participants compared to placebo for acute mania.^{36, 103} Using data available to pool from one RCT and two individual RCTs reported in the meta-analysis, lithium improved manic symptoms essentially to the level of MID (YMRS, MD 5.81, 95% CI 2.21, 9.4; n=643). Withdrawal rates did not differ by group. Serious adverse events were inconsistently reported and showed mixed results.

Lithium Alone Versus Active Control

Evidence was insufficient for all outcomes from one RCT (n=270) to address whether lithium was better for acute mania than divalproex in adults with BD-I, due to a single study and imprecise data.¹²⁶ The study reported response rate, symptoms (YMRS), CGI, and withdrawals did not differ between groups. One of two measures of remission showed benefit for divalproex. No differences in frequency of serious adverse events between groups were noted.

Evidence was insufficient for all outcomes from one small RCT (n=30) to address whether lithium was better than haloperidol, due to a single study and imprecise data.⁹⁶ The study reported no differences between groups in manic symptoms (YMRS) and CGI. Serious adverse events were not reported.

Risperidone versus lithium and risperidone versus haloperidol comparisons are discussed in the risperidone subsection of the antipsychotics section above. Also discussed above in the antipsychotics section are olanzapine versus lithium and quetiapine versus lithium. Overall, while all comparisons were assessed as having insufficient evidence, studies generally reported no differences between the antipsychotic drug and lithium.

(The topiramate comparisons will be discussed in the following section.)

Drugs Not Approved by FDA for Acute Mania in Bipolar Disorder

Key Points

- Ten drugs were examined for acute mania in BD: allopurinol, celecoxib, donepezil, dipyridamole, endoxifen, gabapentin, paliperidone, tamoxifen, topiramate, and oxcarbazepine, some in combination with mood stabilizers.
- Low-strength evidence showed paliperidone improved manic symptoms over placebo in adults with BD-I, although the improvement was not a clinically important difference (n=763). Participants using 12 mg paliperidone reported more common akathisia and dystonia.
- Low-strength evidence showed topiramate was not significantly different from placebo for symptom improvement, and participants using placebo withdrew less for adverse events (n=876) in adults with BD-I. In addition, low-strength evidence showed lithium significantly improved manic symptoms compared to topiramate (n=453) in adults with BD-I, although participants receiving lithium withdrew more for adverse events.
- Low-strength evidence showed allopurinol plus mood stabilizers/other psychotropic medications did not differ significantly from mood stabilizers alone for manic symptom or CGI improvement or overall withdrawals (n=355) in adults with BD-I.
- Evidence was largely insufficient to draw conclusions for all other nonapproved FDA drugs for BD-I for the primary outcomes of interest (response, symptom scores, and function).

Eligible Studies for Drugs Not Approved by FDA

Sixteen unique studies examined nine other drugs for patients experiencing manic events.^{35, 103, 128-141} Four studies were assessed as low risk of bias,^{103, 129, 130, 135} ten were moderate,^{128, 132, 134, 136, 137, 139-141} and four were assessed as high.^{35, 131, 133, 138} Three additional studies were excluded for greater than 50 percent attrition.¹⁴²⁻¹⁴⁴ Eight studies were funded or assisted by industry.^{35, 103, 128, 135, 138-141} All but three studies^{128, 138, 139} used a placebo comparator. Sample sizes ranged from 27 to 876. [Appendix G](#) provides detailed evidence tables, a summary of risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes. A summary of findings with at least low-strength evidence for other drugs not approved by FDA for acute mania are provided in Table 26. Any intervention and comparison not listed in Table 26, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 26. Summary of findings with at least low-strength evidence for drugs not approved by FDA for acute mania

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Paliperidone vs. placebo	2 RCT ^{140 35} (n=763) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): Favors Paliperidone (possible dose response: No difference at 3 and 6 mg, benefit at 12 mg or median dosage of 9 mg) Withdrawal (AE): No difference	Low (moderate study limitations, imprecise)
Topiramate vs. placebo	1 IPD ¹⁰³ (n=876) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): No difference Withdrawals (Overall): Favors Placebo, 37.2% vs. 26.8%, p=0.005 Withdrawals (AE): Favors Placebo, 6.04% vs. 2.84%, p=0.049	Low (moderate study limitations, imprecise)
Topiramate vs. lithium	1 IPD ¹⁰³ (n=453) 3 weeks	YMRS: Favors Lithium, MD 6.14 (95% CI 3.94, 8.34; MID 6)	Low (moderate study limitations, imprecise)
	1 IPD ¹⁰³ (n=453) 3 weeks	Withdrawal (Overall, AE): No difference	Low (moderate study limitations, imprecise)
	1 IPD ¹⁰³ (n=453) 3 weeks	Withdrawal (AE): Favors Topiramate, 2.65% vs. 7.49%, p=0.019	Low (moderate study limitations, imprecise)
Allopurinol + lithium vs. placebo + lithium	4 RCT ^{130 131 132 136} (n=355) 4 weeks	YMRS, CGI, Withdrawal (Overall): No difference	Low (moderate study limitations, imprecise)

AE=adverse events; CGI=clinical global improvement; CI=confidence interval; IPD=Individual patient data; MD=mean difference; MID=minimally important difference; n=number; RCT=randomized controlled trial; YMRS=Young mania rating scale

Table 27 summarizes the bipolar type and major inclusion and exclusion criteria for each study.

Table 27. Population and inclusion criteria for drugs not approved by FDA for acute mania

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Jahangard, 2014 ¹³⁰ Singlesite Iran Low ROB 24953766	I: Allopurinol + valproate and benzodiazapine s C: Placebo+ valproate and benzodiazapine s	BD-I; DSM-IV	Mean Age NR (18-40) Female NR Race NR N=60	Manic; YMRS ≥ 28	Schizoaffective Substance Abuse Other Mental Health Pregnant/Nursing

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Weiser, 2014 ¹³¹ Multisite Israel High ROB 24712840	I: Allopurinol + mood stabilizers C: Placebo+ mood stabilizers	BD-I; DSM-IV	Mean Age 47 (18-65) 66% Female 100% White N=180	Manic; Clinical Interview in DSM-IV treated with mood stabilizer or neuroleptics for between 3 days and 2 weeks.	None Specified
Fan, 2012 ¹³² Singlesite United States Moderate ROB 22420596	I: Allopurinol + current psychiatric medications C: Placebo+ current psychiatric	BD-I; DSM-IV	Mean Age 43 (NR) 50% Female 63% White N=27	Manic; YMRS ≥ 14 partial response to lithium, valproate, carbamazepine, or atypical antipsychotics	Substance Abuse Other Mental Health Pregnant/Nursing Labs/Other Conditions
Machado-Vieira, 2008 ¹³⁶ Multisite Brazil Moderate ROB 18681754	I1: Allopurinol + Lithium I2: Dipyridamole + Lithium C: Placebo + Lithium	BD-I; DSM-IV	Mean Age 29 (18-65) 57% Female Race NR N=180	Manic; YMRS ≥ 22	Schizoaffective Substance abuse Other mental health Taking other meds Labs/other conditions
Arabzadeh, 2015 ¹²⁹ Multisite Iran Low ROB 26291962	I: Celecoxib C: Placebo	BD-I; DSM-IV	Mean Age 31 (18-50) 35% Female Race NR N=48	Manic; YMRS ≥ 20	Schizoaffective Substance abuse Other mental health Taking other meds Labs/other conditions
Chen, 2013 ¹³⁷ Single Site China Moderate ROB 23807849	I: Donepezil +Lithium C: Placebo + Lithium	BD-I; NR	Mean Age 34 (18-65) 40% Female Race NR N=30	Manic; YMRS > 20	Schizoaffective Substance abuse Other mental health Taking other meds Pregnant/nursing Labs/other conditions
Astaneh, 2012 ¹³³ Singlesite Spain High ROB 22978083	I: Gabapentin + Lithium C: Placebo + Lithium	BD-I; DSM-IV	Mean Age NR About 50% Female Race NR N=60	Manic; Not Defined	Substance abuse
Ahmad, 2016 ¹²⁸ Multisite India Low ROB 27346789	I Endoxifen C: Divalproex	BD-I DSM-IV	Mean Age 37 (18-65) Female NR Race 100% Asian N=84	Manic/Mixed; YMRS ≥ 20 and CGI-S ≥ 4	New diagnosis Labs/other conditions Pregnant/nursing

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Yildiz, 2008 ¹³⁴ Single site Turkey Moderate ROB 18316672	I: Tamoxifen C: Placebo	BD-I; DSM-IV	Mean Age 33 (18-60) 52% Female Race NR N=66	Manic; YMRS \geq 20	Schizoaffective Substance abuse Other mental health Neurological disorders Taking other meds Pregnant/nursing
Kushner, 2006 ¹⁰³ Multisite 6 Continents Low ROB 16411977	I: Topiramate C1: Placebo C2: Lithium	BD-I; DSM-IV	Mean Age 41 (16 and up) 51% Female 75% White N=876	Manic/Mixed; YMRS \geq 20	First Manic Episode Schizoaffective Substance abuse Other mental health Taking other meds Pregnant/nursing Labs/other conditions
Chengappa, 2006 ¹³⁵ Multisite US Low ROB 17196048	I: Topiramate + Valproate or Lithium C: Placebo + Valproate or Lithium	BD-I; DSM-IV	Mean Age 40 (18-70) 56% Female 84% White N=287	Manic/Mixed; YMRS \geq 18	Substance abuse Other mental health Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions
Bahk, 2005 ¹³⁸ Multisite South Korea High ROB 15610953	I: Topiramate + Risperidone C: Divalproex + Risperidone	BD-I DSM-IV	Age 37 (18-65) 51% Female Race Asian N=74	Manic; YMRS \geq 20	Other mental health Pregnant/nursing Labs/other conditions Taking other meds
Berwaerts, 2012 ¹³⁹ Multisite 5 Continents Moderate ROB 22377512	I: Paliperidone ER C: Olanzapine	BD-I; DSM-IV	Mean Age 40 (18-65) 52% Female 62% White N=766	Manic/Mixed; YMRS \geq 20	First manic episode; Schizoaffective; Other mental health; Neurological disorders; Taking other meds; Pregnant/nursing; Labs/Other conditions
Berwaerts, 2012a ¹⁴⁰ Mutisite 3 Continents Moderate ROB 20624657	I: Paliperidone ER C: Placebo	BD-I; DSM-IV	Mean Age 40 (18-65); 47% Female 50% White N=469	Manic/Mixed; YMRS \geq 20 with 1 manic or mixed episode in past 3 years	Schizoaffective; Substance abuse; Other Mental Health Condition; Taking other medications; Pregnant/Nursing
Vieta, 2010 ³⁵ Multisite 4 Continents High ROB 20565430	I: Paliperidone ER C1: Placebo C2: Quetiapine	BD-I; DSM-IV	Mean Age 39 (18-65) 42% Female 68% White N=493	Manic/Mixed; YMRS \geq 20	First Manic Episode Schizoaffective Substance abuse Other mental health Neurological disorders

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
					Labs/other conditions
Berwaerts, 2011 ¹⁴¹ Multisite 3 Continents Moderate ROB 20947174	I: Paliperidone ER + Lithium OR Valproate C: Placebo + Lithium OR Valproate	BD-I; DSM-IV	Mean Age 40 (18-65) 46% Female 77% White N=300	Manic/Mixed; YMRS ≥ 20	First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health Conditions; Neurological Disorders; Taking other medications; Pregnant/Nursing

BD=Bipolar Disorder; C=Comparison; CGI-S=Clinical Global Impression, severity; DSM-IV=Diagnostic and Statistical Manual Fourth Edition; ER=Extended Release; FDA=Federal Drug Administration; I=Intervention; N=number; NR=Not Reported; ROB=risk of bias; YMRS=Young Mania Rating Scale

Drugs Not Approved by FDA Versus Placebo

Twelve unique trials^{35, 129-137, 140, 141} and one pooled analysis of a further four trials¹⁰³ examined nine drugs versus placebo. Five studies examined the drugs as a single drug,^{35, 103, 129, 134, 140} while eight were added to mood stabilizers or other current psychiatric medications.^{130-133, 135-137, 141} Studies ranged from 3 to 12 weeks long. All enrolled BD-I participants.

Low-strength evidence (moderate study limitations, imprecision) from two studies (n=763) showed paliperidone was better than placebo for improvement in mania symptoms (YMRS).^{35, 140} However, for the highest dose of 12 mg in the moderate risk of bias study, the improvement may not be clinically meaningful based on values that are less than the MID. The study reported YMRS mean difference of 3.4 (p=0.025), which is less than the MID of 6. While a dose response was suggested, authors stated results were driven largely by participants in India, who comprised only 10 percent of the analysis set. Low-strength evidence (moderate study limitations, imprecision) showed no statistically significant differences between groups for withdrawal for lack of efficacy. Evidence for CGI and response and remission rates was insufficient due to moderate study limitations, inconsistency, and imprecision. With the exception of more common akathisia and dystonia EPS symptoms for 12 mg paliperidone versus placebo, no differences in serious adverse events were noted [Appendix G](#) provides further detail.

Topiramate versus placebo was examined in a pooled analysis of four trials (n=876).¹⁰³ Low-strength evidence (high imprecision) showed no differences between topiramate and placebo for manic symptoms (YMRS) or withdrawal due to lack of efficacy for adults with BD-I. Additionally, overall withdrawals and withdrawals due to adverse events were lower in the placebo group (low-strength evidence, high imprecision). No differences in severe adverse events between groups were reported. [Appendix G](#) provides further detail.

Evidence was insufficient for all outcomes for the two drugs [celecoxib](#)¹²⁹ and [tamoxifen](#),¹³⁴ examined as single drug versus placebo for acute mania, due to single studies and imprecision.

For adjunctive medications, low-strength evidence (moderate study limitations, imprecision) from four RCTs (n=355) showed no significant differences between allopurinol plus mood stabilizers compared to mood stabilizers alone in manic symptoms (YMRS), CGI, or overall withdrawals.^{130-132, 136} Evidence was insufficient for response (high study limitations, imprecision)^{131, 136} and remission (moderate study limitations, inconsistent, imprecision) rates.^{130, 136} No serious adverse event were reported. [Appendix G provides further detail.](#)

Evidence was insufficient for all outcomes for [dipyridamole](#),¹³⁶ [donepezil](#),¹³⁷ or [gabapentin](#)¹³³ plus lithium versus placebo largely due to single studies and imprecision. Evidence was also insufficient for all outcomes for one study of [topiramate](#) plus mood stabilizers versus mood stabilizers alone, although the general finding of no significant differences between groups was similar to the findings for topiramate as single drug.¹³⁵ Likewise, one study of [paliperidone](#) plus mood stabilizers, while in itself providing insufficient evidence, repeated the general finding of no significant differences between groups observed in comparison of paliperidone as monotherapy versus placebo.¹⁴¹

Drugs Not Approved by FDA Versus Active Control

Six trials examined drugs versus active comparators in BD-I participants, each a unique comparison.^{35, 103, 136, 138, 139} Study sizes ranged from 30 to 388 and ran from 3 to 12 weeks.

Low-strength evidence (high imprecision) from a pooled analysis of individual patient data from two trials (n=453) of [topiramate](#) versus lithium for adults with BD-I with acute mania showed manic symptoms (YMRS) improved more with lithium and the difference was at the MID level (6.14, 95% CI 3.94, 8.34).¹⁰³ Overall withdrawals and withdrawals due to lack of efficacy did not differ between groups (low-strength evidence). However, less participants receiving topiramate withdrew due to adverse events (7% vs. 3%). There were no differences in severe adverse events between lithium and topiramate groups.

Evidence was insufficient for all outcomes to address if [endoxifen](#) was better for acute mania in adults with BD-I than divalproex (unknown consistency, imprecise),¹²⁸ or if [paliperidone](#) extended release was better than olanzapine¹³⁹ or quetiapine (high study limitations, unknown consistency, imprecise).³⁵

Evidence was insufficient for all outcomes to address if [allopurinol](#) plus lithium was better for acute mania in adults with BD-I than dipyridamole plus lithium (moderate study limitations, unknown consistency, imprecise), or if topiramate plus risperidone was better than divalproex plus risperidone (high study limitations, unknown consistency, imprecise).¹³⁸

Interpreting the Findings for Drugs for Acute Mania

All FDA-approved antipsychotics, except aripiprazole, when compared to placebo improved mania symptoms for adults with BD-I (low-strength evidence). For four of the antipsychotics we were able to provide a point estimate. Lithium also reached low-strength evidence for improving mania symptoms, however, studies for carbamazepine, divalproex/valproate, and lamotrigine failed to reach sufficient evidence due to too few studies and imprecise results. Likewise, evidence was insufficient to draw conclusions for the efficacy of antipsychotics added to mood stabilizers.

Except for the finding that lithium improved mania symptoms better than topiramate (low-strength evidence), evidence from studies of drugs compared to other drugs, whether as single

drug or drug combinations, for treatment of acute mania was also insufficient to draw conclusions. Our ability to draw conclusions was hampered by the small number of studies and sample sizes to allow confidence in findings of no differences between groups. Study designs generally tested for superiority of one drug over the other, rather than noninferiority of the two drugs. With noninferiority tests, if the relative equivalence of the performance of two drugs is not demonstrated strongly enough, nonequivalence cannot be ruled out; that is, the treatment effects of the two drugs are too different.

Only two small studies attempted to address efficacy and harms for specific populations of interest, pregnant women with BD (lamotrigine), and BD patients with hypomania (quetiapine). Unfortunately, results for the effect of quetiapine treatment for patients with hypomania were not reported separately from patient with mild mania, thus no conclusions can be made. Similarly, the single observational study for pregnant women provided insufficient evidence to address whether lamotrigine provided benefits. Because of the weak evidence, there was little to be gained from the very few studies that did attempt post-hoc analysis of subgroups. Post-hoc analyses cannot reach the same level of strength of evidence due to the inherent higher study limitations from studies that generated low-strength evidence for main findings would . Given the generally high levels of attrition observed in the included studies, results of any subgroup analysis of such a restricted set are even more suspect.

Adverse events were somewhat consistently reported for extrapyramidal symptoms, and clinically significant weight gain of greater than 7 percent, but otherwise variably reported. The harms findings from the included placebo-controlled studies were consistent with information currently reported by FDA labels. While most studies reported no differences between groups in studies comparing drugs to drugs, we noted a general pattern of participants receiving atypical antipsychotics experiencing fewer extrapyramidal symptoms than participants receiving other medications.

The seventeen studies examining efficacy and comparing drugs to drugs of ten other medications, either as single drug or added to other psychiatric medications, largely yielded insufficient evidence due to a single study for each specific comparison, small sample sizes, and/or inconsistent findings.

There were a few exceptions, such as a low-strength evidence that lithium improved manic symptoms more than topiramate, although topiramate had lower rates of withdrawal due to adverse events than lithium. There was also low-strength evidence for no group differences in examined outcomes for topiramate versus placebo and allopurinol plus mood stabilizers/lithium/other psychiatric medications versus these other medications alone. Low-strength evidence supported that paliperidone improved manic symptoms more than placebo, although the improvement was not clinically significant since it did not reach the MID.

Several issues impact the applicability of the studies. Over three quarters of the studies also excluded participants experiencing a first manic episode and most enrolled participants were 30 to 50 years of age. Moreover, given the inclusion criteria and actual participant characteristics, it is not clear if the current findings extend to populations with first manic episodes, current comorbid substance use, or pregnant or nursing women with BD I, or older adults with BD-I.

Chapter 5. Drug Treatments for Depression

Key Points

- Evidence for treatment of depression in adults with bipolar disorder (BD) with at least 3 months followup was very sparse.
- The effects of four drugs compared with placebo: memantine, lamotrigine, or antidepressants (paroxetine, bupropion, or both) and two drugs compared with other drugs: sertraline or venlafaxine were examined for depression in BD.
- Evidence was largely insufficient to draw conclusions regarding the effects of drug treatments for depression in adults with BD for the primary outcomes of interest (relapse, symptom scores, and function).

Eligible Studies for Depression Treatments

We identified 11 eligible publications reporting seven unique randomized controlled trials (RCTs) of drug treatments for depression in adults with BD with at least 3 months followup.¹⁴⁵⁻¹⁵⁴ Two studies were assessed as moderate risk of bias and four were assessed as high. One additional study was excluded for greater than 50 percent attrition.¹⁵⁵ All studies were funded in whole or part by government sources. No studies for lurasidone, olanzapine, or quetiapine, Federal Drug Administration (FDA)-approved for depression in BD, met the inclusion criteria of at least 3 months followup. Three interventions were compared to placebo¹⁴⁷⁻¹⁵⁰ and added to mood stabilizers while three were single drugs versus active comparators.^{33, 151-154} Sample sizes ranged from 49 to 366. Also discussed is an additional RCT examining lithium in participants with BD with at least mild symptoms needing clinical care, as the majority of participants were experiencing depression symptoms.¹⁵⁶

Table 28 summarizes the bipolar type and major inclusion and exclusion criteria for each study. [Appendix H](#) provides detailed evidence tables, a summary of risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes.

Table 28. Population and inclusion criteria for studies of drug treatments for depression

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Lee, 2014 ^{148, 149} Multisite China High ROB 24103632 23870798	I: Memantine + Valproic Acid C: Placebo + Valproic Acid	Modified BD-II; 2- days hypomanic (versus 4 in DSM-IV criteria)	Mean Age 32 (All ages); 49% Female; Race (Taiwan) N=232	Depressed; HAM-D≥18	Schizoaffective Substance abuse Other mental health Neurological disorders Taking other medications
Kemp, 2012 ¹⁴⁷ Singlensite US Moderate ROB 23107222	I: Lamotrigine + mood stabilizer C: Placebo + mood stabilizer	Rapid cycling BD-I or II DSM-IV	Mean Age 38 (16-65) 56% Female; White 92% 55% BD-I 45% BD-II N=49	Major Depressive Episode (did not stabilize on open treatment of lithium and divalproex)	Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds (nonresponsive to lamotrigine previously)

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Sachs, 2007 ¹⁵⁰ Multisite US High ROB 17392295	I: antidepressant (paroxetine, bupropion, or both) + mood stabilizer C: Placebo + mood stabilizer	BD-I or II DMS-IV	Mean Age 40 (18+) 57% Female Race 10% Nonwhite 68% BD-I 32% BD-II N=366	Major Depressive Episode	Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions
Altshuler, 2017 ¹⁵¹ Multisite US High ROB 28135846	I: Sertraline C1: Lithium C2: Lithium + Sertraline	BD-II DSM-IV	Mean Age 39 (18-65) Female 54% White 97% BD-II 100% N=142	Current major depressive episode. IDS-C \geq 22; CGI-BD \geq 3 on depression subscale; YMRS \leq 8; CGI-BD=1 on mania severity subscale	Substance Abuse Other Mental Health (Nonresponsive to Lithium or Sertraline)
Amsterdam, 2016 ^{152, 153} Singlensite US Moderate ROB 26892848 26803764 ¹⁵³	I: Venlafaxine C: Lithium	BD-II DSM-IV	Mean Age 43 (18+) Female 57% White 73% BD-II 100% N=129	Current major depressive episode. HAM-D \geq 16	Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds Labs/Other Conditions (Nonresponsive to Venlafaxine or Lithium)
Amsterdam, 2008 ^{145, 154} Singlensite US High ROB 18344727 18486235 ¹⁵⁴	I: Venlafaxine C: Lithium	BD-II DSM-IV	Mean Age 37 (18+) Female 57% White 82% BD-II 100% N=83	Current major depressive episode. HAM-D \geq 18	Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds Labs/Other Conditions (Nonresponsive to Venlafaxine or Lithium)
Nierenberg, 2013 ^{146, 156} Multisite US Low ROB 23288387 19933719	I: Lithium + Optimal Personalized Treatment (OPT) C: Optimal Personalized Treatment	BD-I or II; DSM-IV	Mean Age 39 (18+) 57% Female 75% White 76% BD-I 24% BD-II N = 283	Currently symptomatic (not defined), requiring a change in medication (Mean YMRS 12.5; MADRS 22.5; CGI severity 4.3)	Current lithium use Need for hospitalization Other Medical Conditions Pregnancy

BD=bipolar; C: Control; CGI=Clinical global impression scale; DSM-IV= Diagnostic and statistical manual, 4th edition; HAM-D= Hamilton Rating Scale for Depression; I=Intervention; IDS-C=Inventory of depressive symptomatology – clinician rated; MADRS= Montgomery Asberg depression rating scale; N=number; NR=not reported; ROB=risk of bias; YMRS=Young Mania Rating Scale.

Drug Treatments for Depression Versus Placebo

Strength of evidence from three RCTs was insufficient to draw conclusions for the effect of depression treatments compared to placebo in adults with BD due to single studies and

imprecision. Each study with a placebo comparator addressed a different intervention for a different bipolar population; [memantine](#) versus placebo in adults with bipolar II disorder (BD-II),^{148, 149} [lamotrigine](#) versus placebo in adults with rapid cycling BD-II,¹⁴⁷ and [antidepressants](#) versus placebo in adults with bipolar I disorder (BD-I) and BD-II.¹⁵⁰ All three studies reported no significant differences between groups for all outcomes. Information on adverse events was reported in two studies. Both reported no differences between groups for severe adverse events or withdrawal due to a lack of response or clinical worsening.^{147, 150}

Drug Treatments for Depression Versus Active Control

Strength of evidence from three RCTs was assessed as insufficient to draw conclusions for depression treatments compared with other drugs in BD due to study limitations and imprecision. The three studies with active comparators addressed two comparisons for adults with BD-II and a current major depressive episode: a three arm study of [sertraline versus lithium or lithium plus sertraline](#),¹⁵¹ and two studies of [venlafaxine versus lithium](#).^{150, 153} Reported results were mixed for treatment response or remission. All three studies assessed switching to hypomanic or manic states but found no significant differences between groups. Only one unidentified serious adverse event was reported across the three studies' total of 354 participants.

Lithium Plus OPT Versus OPT Alone

One pragmatic RCT enrolled 283 participants with BD-I or II who were at least mildly symptomatic, with clinical need, and randomized them to receive moderate-dose lithium plus Optimized Personalized Treatment (OPT) or OPT alone.¹⁵⁶ OPT follows the Texas Implementation of Medication Algorithm, so participants were commonly using medications other than lithium. While the population was not specifically identified as experiencing a manic state, and in fact 87 percent of the participants were experiencing a depressive state, the participants were not clinically stable and treatment was deemed necessary to stabilize mood. Evidence for all outcomes was deemed insufficient due to a single study with too small of a sample size to test the finding of no difference between groups in CGI or need for clinical treatment adjustment. The study was not designed to test for nonsignificance between groups. The study reported fewer participants in the lithium group needed less atypical antipsychotics than those in the OPT-only group (48.3 percent and 62.5 percent, respectively). [Appendix H](#) provides details.

Interpreting the Findings for Drug Treatments for Depression

Evidence for drug treatment for BD depression is insufficient to draw conclusions. Only six RCTs that examined five unique comparisons for bipolar depression met inclusion criteria. These studies differed in their diagnostic inclusion criteria, but tended to recruit predominantly individuals with BD II or mixed samples of BD-I and BD II without examining the effectiveness of treatments separately for each bipolar subtype. Given clinicians' concerns about treatment-induced switching into hypomania/mania and other adverse events, it is notable that not all studies systematically reported adverse events. The few studies that did report adverse events tended to find no group differences. Additional evidence is necessary to draw definitive conclusions about adverse events of drug treatments for bipolar depression.

The degree and nature of the sparse and scattered studies is noteworthy. Often studies did not meet the review's inclusion criteria of at least three month followup for depression, including studies for lurasidone, olanzapine, or quetiapine, which are FDA-approved for depression in BD.

Given the chronic nature of BD, it is doubtful that studies reporting effects for drugs with followup periods shorter than 3 months are clinically useful.

Chapter 6. Drug Treatments for Maintenance

Key Points

- Evidence for maintenance treatments was scattered across 16 drugs administered alone or in combination therapy.
- Evidence was largely insufficient to draw conclusions regarding the effects of drug treatments for maintenance of euthymia in adults with bipolar disorders (BD) for the primary outcomes of interest (relapse, symptom scores, and function).
- Low-strength evidence showed longer time to recurrence of any mood state for bipolar I disorder (BD-I) patients receiving lithium compared to placebo (n=1579) in followup up to 2 years. Participants receiving lithium reported more tremor than those receiving placebo.
- Evidence was insufficient for all other outcomes across all interventions.

Eligible Studies for Maintenance Treatments

We identified 44 eligible publications reporting 36 unique studies with at least 6 months followup.^{56, 139, 157-192} Twenty-one studies, seven of which were three-arm studies, examined a single drug treatment for maintenance,^{56, 82, 99, 117, 124, 139, 160, 161, 164, 165, 167-173, 176, 178, 180, 181, 184, 187, 190, 191} and 16 examined drug combinations.^{88, 116, 160, 162, 163, 166, 174, 175, 177, 179, 182, 183, 185, 186, 188, 189, 192} Drugs examined included: oral aripiprazole, long-acting injectable aripiprazole, divalproex/valproate, carbamazepine, fluoxetine, gabapentin, lamotrigine, lithium, olanzapine, oxcarbazepine, paliperidone, perphenazine, long-acting injectable risperidone, quetiapine, venlafaxine, and ziprasidone. Fourteen studies were assessed as low or moderate risk of bias and 22 were assessed as high, generally due to attrition. Of 36 unique studies, 27 were industry funded. An additional 15 studies were excluded due to attrition over 50 percent and not using time to relapse outcomes.^{74, 75, 81, 83, 86, 87, 95, 115, 119, 120, 123, 125, 193-196} Only two studies were not RCTs.^{176, 185} Sample sizes ranged from 25 to 1226; 17 studies were below 200 participants, ranging from 25 to 175. Study duration ranged from 6 months to 3 years, with 24 using followup of 6 months to 1 year.

[Appendix I](#) provides detailed evidence tables, summary risk of bias assessments, and assessments of strength of evidence for key comparisons and outcomes. A summary of findings with at least low-strength evidence for other drug treatments for maintenance are provided in Table 29. Any intervention and comparison not listed in Table 29, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 29. Summary of findings with at least low-strength evidence for maintenance studies

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Lithium vs. placebo	6 RCT ^{165 167 162 164 178 187} (n=1579) 1 to 2 years	Time to overall relapse: Favors Lithium	Low (moderate study limitations, imprecise)

n=number; RCT=randomized controlled trial

Single Drug Treatments for Maintenance

Table 30 summarizes the bipolar type and major inclusion and exclusion criteria for single drug studies for maintenance. [Appendix I](#) provides details.

Table 30. Population and inclusion criteria for single drug studies for maintenance

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Calabrese, 2017 ¹⁹¹ Multisite 4 Continents Moderate ROB 28146613	I: Long-acting Aripiprazole (monthly injection) C: Placebo	BD-I; DSM-IV	Mean Age 41 (18-65); Female 58%; Race 54% Black/African American 28% N=266	Initial manic episode YMRS ≥ 20 but then met YMRS ≤ 12 , MADRS ≤ 12 , no active suicidality	Rapid Cycling Refractory BD First Manic Episode Substance Abuse Other Mental Health Labs/Other Conditions
Keck, 2006 ⁵⁶ Multisite 2 Continents Moderate ROB 16669728	I Aripiprazole C: Placebo	BD-I DSM-IV	Mean Age 40 (18+); Female 67% Race White 56% Hispanic/Latino 23% N=161	Symptom stability: YMRS ≤ 10 and MADRS ≤ 13 for 4 consecutive visits over 6 weeks	Substance Abuse Other Mental Health Labs/Other Conditions Pregnant/Nursin g Unresponsive to Clozapine ECT in last 2 years
Greil, 1997 ¹⁷¹ Multisite Germany High ROB 9165384 9864077 ¹⁷⁰ 10529070 ¹⁶⁹ 10529071 ¹⁶⁸ 11093063 ¹⁹⁰	I: Carbamazepine C: Lithium	BD-I or II; DSM-IV	Mean Age 40 (18-65); Female 57%; Race NR BD I 58% BD-NOS 33% N=171	Remission from any bipolar episode; GAS > 70	First Manic Episode Substance Abuse Other Mental Health Neurological Disorders
Hartong, 2003 ¹⁷³ Multisite Netherlands Low ROB 12633122	I: Carbamazepine C: Lithium	BD-I or II; DSM-III	Mean Age 42 (18+); Female 54%; Race NR BD I 77% BD-II 23% N=98	Remission from any bipolar episode, according to Bech Rafaelsen Mania or Melancholia Scales	First Manic Episode

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Bowden, 2003 ¹⁶⁵ Multisite 3 continents Moderate ROB 12695317	I: Lamotrigine C1: Placebo C2: Lithium	BD-I; DSM-IV	Mean Age 41 (18+); Female 47%; Race NR N=175	Lamotrigine responders (CGI- S _≤ 3 for at least 4 continuous weeks), after an open label period: Manic; DSM- IV Criteria for Mania or Hypomania currently or within past 60 days with previous episodes in past 3 years.	Other Mental Health Conditions
Calabrese, 2003 ¹⁶⁷ Multisite 4 Continents Moderate ROB 14628976	I: Lamotrigine C1: Placebo C2: Lithium	BD-I; DSM-IV	Mean Age 43 (18+); Female 56%; Race NR N=410	Lamotrigine responders (CGI- S _≤ 3 for at least 4 continuous weeks) after an open label period: depression; DSM-IV criteria for depression currently or within past 60 days with previous depression and mania episodes in past 3 years.	Other Mental Health Conditions
Calabrese, 2000 ¹²⁴ Multisite US, Canada High ROB 11105737	I: Lamotrigine C: Placebo	Rapid cycling BD-I or II DSM-IV	Mean Age 38 (18+); Female 58% Race NR BD I 70% BD-II 30% N=182	Rapid cyclers, stabilized on lamotrigine (no mood episodes requiring other drugs or ECT)	Other Mental Health Conditions Labs/Other conditions
Amsterdam, 2010 ¹⁶² Single-Site US Moderate ROB 20360317	I: Fluoxetine C1: Placebo C2: Lithium	BD-II; DSM-IV	Median Age 38 (18+); Sex NR; Race NR N=81	Recovered; HAM-D _≥ 16 at enrollment; HAM-D _≤ 8 after 12 weeks of initial Fluoxetine therapy at 20-80mg/day)	Substance abuse Neurological Disorders Taking other medications Pregnant/Nursin g Labs/Other Conditions
Calabrese, 2005 ¹¹⁷ Single-site US Government High ROB 16263857	I: Divalproex C: Lithium	Rapid cycling BD-I or II DSM-IV	Mean Age 37 (18+) Female 52% White NR BD I 60% BD-II 40% N=60	Responders to both drugs Rapid cycling; mood episode in previous 3 months	Substance Use Other Mental Health Conditions Pregnant/Nursin g Lab/other conditions Intolerant of lithium

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Bowden, 2000 ¹⁶⁴ Multisite US Moderate ROB 10807488 12784116 ¹⁷²	I: Divalproex C1: Placebo C2: Lithium	BD-I; DSM-III	Mean Age 39.2 (18-75); Female 51%; White 94% N=372	No episode at randomization; Scores of YMRS ≤ 11, DSS ≤ 13, GAS > 60;	Substance Abuse; Other Mental Health Conditions; Taking Other Medications; Pregnant/Nursin g
Newport, 2008 ¹⁷⁶ Single site US High ROB 18402631	I: Lamotrigine C: Discontinued mood stabilizers	BD-I, II or NOS; DSM-IV	Mean Age Female 100% White 91% BD I 73% BD-II 23% BD-NOS 4% N=26	Euthymic; at conception of current pregnancy	Labs/Other Conditions
Prien, 1973 ¹⁷⁸ Multisite US High ROB 4569674	I: Lithium C: Placebo	BD-I; NR	Median Age 44 (17-60); Sex NR; Race NR N=205	No episode at randomization;	Neurological Disorders; Abnormal Lab Results
Balance Investigators, 2010 ¹⁶⁰ Multisite 2 Continents Moderate ROB 20092882	I: Lithium + Valproate C1: Lithium C2: Valproate	BD-I; DSM-IV	Mean Age 43 (16+); Female 49%; Race NR (U.S.A and Europe) N=330	Not having acute episode ; not defined	Pregnant/Nursin g
Tohen, 2006 ¹⁸⁰ Multisite 2 Continents Moderate ROB 16449478	I: Olanzapine C: Placebo	BD-I; DSM-IV	Mean Age 40 (18+); Female 39%; White 87% N=361	Remission from manic or mixed episode; YMRS ≤ 15 and HAM-D ≤ 8	First Manic Episode
Tohen, 2003 ⁸² Multisite US High ROB 12832240 Extension of Tohen, 2002b ⁴⁴ 12042191	I: Olanzapine C: Divalproex	BD-I DSM-IV	Mean Age 40 (18-75) Female 57% White 82% N=251	YMRS >19 (time to relapse; not clear what proportion were stable)	Substance Use Pregnant/Nursin g Labs/other conditions
Vieta, 2012 ¹⁸⁴ Multisite 4 Continents High ROB 22503488	I: Olanzapine C1: Placebo C2: Risperidone	BD-I; DSM-IV	Mean Age 37 (18-65); Female 52%; White 41% N=398	No current episode; responders from Phase II Acute (YMRS ≥ 20 and CGI-S ≥ 4) or non- acute (mood episodes with YMRS < 12 and CGI-S ≤ 3)	First Manic Episode Schizoaffective Other Mental Health Taking Other Meds Pregnant/Nursin g

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demographics	Current Episode	Key Exclusions
Tohen, 2005 ¹⁸¹ Multisite 5 Continents Moderate ROB 15994710	I: Olanzapine C: Lithium	BD-I; DSM-IV	Mean Age 42 (18+); Sex 53%; White 99% N=431	Met remission criteria: including YMRS \leq 15 and HAM-D \leq 8 After open-label: Manic or Mixed Episode YMRS \geq 20	Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Labs/Other Conditions
Berwaerts, 2012 ¹³⁹ Multisite 5 Continents High ROB 22377512	I: Paliperidone extended release C: Placebo	BD-I; DSM-IV	Mean Age 40 (18-65); Female 55% White 61% N=383	Remission; YMRS and MADRS \leq 12 for last three weeks of acute and continuation treatment study phases	First manic episode Schizoaffective Substance abuse Other mental health Neurological disorders Labs/other conditions
Quiroz, 2010 ⁹⁹ Multisite 3 Continents Moderate ROB 20227682	I: Risperidone long-acting C: Placebo	BD-I DSM-IV	Mean Age (18- 65) Female 49% White 80% N=303	Responders to Phase III: stable at CGI-BP-S <3	Substance abuse Taking other meds Pregnant/nursing Rapid cycling Other mental health Labs/other conditions
Amsterdam, 2015 ¹⁶¹ Single site US High ROB 26143402	I: Venlafaxine C: Lithium	BD-II; DSM-IV	Mean Age 42 (18+); Female 54%; White 17% N=55	Responders to RCT phase: \geq 50% reduction in baseline HAM-D + CGI-BP-S <3	Substance abuse Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions
Weisler, 2011 ¹⁸⁷ Multisite RCT of responders Multisite 5 continents Moderate ROB 22054050	I: Quetiapine C1: Placebo C2: Lithium	BD-I; DSM-IV	Mean Age 40 (18+) Female 53% White 63% N=1226	Meeting stability criteria of YMRS \leq 12 and MADRS \leq 12; Current or previous depression/mania/mi xed episode at entry or within past two years	Substance Abuse Other Mental Health Conditions Pregnant/Nursin g Labs/Other Conditions

BD=bipolar disorder; C=control; CGI-BP-S=clinical global impression scale, bipolar edition, severity; DSM-IV= Diagnostic and statistical manual, 4th edition; DSS=depression severity scale; ECT= electroconvulsive therapy; EX=extended release; GAS=Global Assessment Scale; HAM-D = Hamilton Rating Scale for Depression; I=intervention; MADRS= Montgomery-Asberg depression rating scale; N=number; NR=not reported; RCT=randomized controlled trial; ROB=risk of bias; YMRS=young mania rating scale.

Single Drug for Maintenance Versus Placebo

Twelve studies examined nine different drugs versus placebo in participants with BD-I.^{82, 99, 117, 124, 139, 161, 164, 165, 167, 178, 180, 184, 187, 191} Five studies also included bipolar II disorder (BD-II)

participants.^{117, 124, 163, 182, 183} Sample sizes ranged from 26 to 1226 and followup lasted from 26 weeks to 3 years.

Low-strength evidence (moderate study limitations, imprecision) from six RCTs (n=1579) showed that adults with BD-I receiving lithium over a 2 year period had longer time to recurrence of any mood state compared to those receiving a placebo.^{179, 186} Since the time to event outcomes account for attrition, these were the only outcomes abstracted from these studies due to the high attrition rates. Evidence was insufficient for time to manic or depressive states due to mixed results. Participants receiving lithium reported more tremor than those receiving placebo. Otherwise serious adverse events did not differ by group. [Appendix I](#) provides details.

Evidence was insufficient for all outcomes to address whether ten drugs were better than placebo for maintenance in adults with BD: long-acting aripiprazole (n=226),¹⁹¹ aripiprazole (n=1610),⁵⁶ divalproex (n=281),^{165, 172} fluoxetine (n=55),¹⁶² lamotrigine (n=471; n=182 rapid cycling),^{124, 164, 167} olanzapine (n=855),^{139, 180, 184} paliperidone (n=300),¹³⁹ quetiapine (n=808),¹⁸⁷ and risperidone (n=353).^{99, 184} Single studies, high study limitations, small sample sizes, and strong imprecision contributed to the insufficient strength of evidence rating. Except for divalproex, results were reported as favoring the interventions for time to overall relapse. Where reported, participants using placebo experience less frequent severe events of tremor than those using divalproex, or less parkinsonism than those using olanzapine; otherwise, serious adverse events were generally not different between groups. [Appendix I](#) provides details.

While providing insufficient evidence to draw conclusions, one observational study was noteworthy for examining lamotrigine use in 26 pregnant women, recruited before conception or during first trimester, with any BD type. Women chose to discontinue all mood stabilizers or to continue on lamotrigine only. While women who chose to continue lamotrigine were less likely to have an unplanned pregnancy than those who discontinued all treatment. Risk of relapse was 3/10 women using lamotrigine versus 16/16 women who discontinued treatment.

Single Drug for Maintenance Versus Active Control

Fourteen studies (20 publications) examined 10 different drugs versus another drug.^{139, 157-162, 164, 165, 167-173, 178, 181, 184, 187, 190} Sample sizes ranged from 54 to 768 and followup lasted from 6 months to 3 years. [Appendix I](#) provides details.

Evidence was insufficient for all outcomes to address whether carbamazepine (n=171),^{168-171, 173, 190} divalproex (n=372, n=60 rapid cycling),^{117, 164, 172} fluoxetine (n=54),¹⁶² lamotrigine (n=390),^{165, 167} olanzapine (n=855),¹⁸¹ quetiapine (n=768),¹⁸⁷ valproate (n=220),¹⁶⁰ and venlafaxine (n=55)¹⁶¹ was better than lithium; paliperidone (n=235)¹³⁹ or risperidone (n=263)¹⁸⁴ was better than olanzapine; or olanzapine was better than divalproex (n=251)⁸² for maintenance in adults with BD. Single studies, high study limitations, small sample sizes, and imprecision contributed to the insufficient strength of evidence rating. Results were mixed across the studies. With the exception of participants using divalproex showing less akathisia compared to those using lithium, no differences between groups were reported for serious adverse events.

Combination Drug Treatment for Maintenance

Table 31 summarizes bipolar type and major inclusion and exclusion criteria for combination drug therapy studies for maintenance. [Appendix I](#) provides details.

Table 31. Population and inclusion criteria for combination drug treatment for maintenance studies

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Woo, 2011 ¹⁸⁸ RCT Multisite Asia High ROB 22134973	I: Aripiprazole + divalproex C: Placebo + divalproex	BD-I; DSM-IV	Mean Age 38 (18-65); Female 68% Asian ≥75% N=83	Remission after Manic/Mixed; Initially YMRS≥20, then YMRS≤12, MADRS≤13 at randomization after 6 weeks of stabilization treatment	Schizoaffective Substance abuse Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions
Marcus, 2011 ¹⁷⁵ RCT Multisite NR High ROB 21443567	I: Aripiprazole + lithium/valproate C: Placebo + lithium/valproate	BD-I; DSM-IV	Mean Age 39 (18+) Female 55% White 68% N=337	Remission after Manic/Mixed; Initially YMRS≥16 and current episode duration <2 years; then YMRS≤12, MADRS≤12 at randomization after 12 weeks of stabilization treatment	First manic episode Schizoaffective Substance abuse Other mental health Neurological disorders Taking other meds Labs/other conditions
Carlson, 2012 ¹⁹² RCT of responders Multisite US Industry High ROB 22329471	I: Aripiprazole + lamotrigine C: Placebo + lamotrigine	BD-I; DSM-IV	Mean Age 39 (18+) Female 65% White 90% N=351	Stabilization after mania; 8 weeks at YMRS≤12, MADRS≤12. Study entry manic or mixed YMRS≥16 in previous 3 months with or without rapid cycling (4 to 7 mood episodes per year)	Substance abuse Other Mental Health Conditions Pregnant/Nursing Labs/other conditions First manic episode Treatment refractory mania/mixed mania
Kemp, 2009 ¹¹⁶ Single site US High ROB 19192457	I: Divalproex + lithium C: Placebo + lithium	BD-I or II; DSM-IV	Mean Age 36 (16-65) Mean Age 36 Female 36% White 82% BD I 75% BD II 25% N=31	Stable responders (HAM-D score ≤ 20, YMRS score ≤ 12.5) Rapid cycling, substance use disorder as ascertained by structured interview; mood episode in previous 3 months	Labs/other conditions Pregnant/nursing

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Vieta, 2006 ¹⁸³ Multisite Spain High ROB 16649836	I: Gabapentin + mood stabilizers C: Placebo + mood stabilizezrs	BD-I or II; DSM-IV	Mean Age 49 (18-75) Female 72% Race NR BD I 76% BD II 24% N=25	Euthymic; CGI-BP-M \geq 4; HAM-D \leq 8 YMRS \leq 4;	Substance abuse Pregnant/nursing Labs/other conditions
Tohen, 2004 ⁸⁸ Multisite US, Canada Industry High ROB 15056579 extension of Tohen, 2002a ⁶⁶ 11779284	I: Olanzapine + Lithium or Valproate C: Placebo + Lithium or Valproate	BD-I; DSM-IV	Mean Age 41 (19-69) 48% Female 85% White N = 99	Responders to olanzapine + lithium or valproate mania and depression no worse than mild;	First Manic Episode Labs/Other Conditions
Vieta, 2008 ¹⁸² Multisite Spain Moderate ROB 18346292	I: Oxcarbazepine + Lithium C: Placebo + Lithium	BD-I or II; DSM-IV	Mean Age 44 (18+); Female 66% Race NR BD I 76% BD II 24% N=55	Euthymic; YMRS \leq 12; MADRS \leq 20	Substance abuse Other Mental Health Conditions Pregnant/Nursing Labs/other conditions
Zarate, 2004 ¹⁸⁹ Singlesite US High ROB 14702269	I: Perphenazine + mood stabilizers C: Placebo + mood stabilizers	BD-I; DSM-IV	Mean Age 34 (18-65); Female 78% White 80% N=37	Remission after Manic /Mixed as defined per DSM- IV criteria (Structured Clinical Interview); then euthymic by week 10 at randomization; YMRS \leq 10; HAM-D \leq 10	Schizoaffective Substance abuse Other mental health Labs/other conditions
Suppes, 2009 ¹⁷⁹ Multisite US/Canada High ROB 19289454	I: Quetiapine + Lithium OR Valproate C: Placebo + Lithium OR Valproate	BD-I; DSM-IV	Mean Age 40 (18+) Female 53%; White 82% N=623	Stabilization after Mania; Stable at randomization after Lithium or Valproate; YMRS and MADRS \leq 12 AND at least 1 mood episode of any type in past 2 years and another 6 months prior to randomization	First Manic Episode Substance Abuse Other Mental Health Conditions Pregnant/Nursing

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Vieta, 2008 ¹⁸⁶ Multisite 4 Continents Moderate ROB 18579216	I: Quetiapine + Lithium OR Valproate C: Placebo + Lithium OR Valproate	BD-I; DSM-IV	Mean Age 42 (18+); Female 55%; White 97% N=706	Stabilization after the latest episode of any type (mania, mixed, depression) within past 26 weeks, then achieved clinical stability (YMRS and MADRS ≤ 12) prior to randomization, subject to specified time periods	Substance Abuse; Other Mental Health Conditions; Taking Other Meds; Pregnant/Nursing
Macfadden, 2009 ¹⁷⁴ Multisite US/India High ROB 19922552	I: Risperidone (long-acting injectable) + Treatment As Usual (mania treatments, anti- depressants, etc.) C: Placebo + Treatment as usual	BD-I; DSM-IV	Mean Age 38.9 (18-63); Female 28%; White 10% N=124	Any current phase including euthymic; 4 or more mood episodes in past year	Substance Abuse; Other Mental Health Conditions; Taking other Medications; Abnormal Lab Results
Bobo, 2011 ¹⁶³ Single-site US High ROB 22104634	I: Risperidone + treatment as usual C: Treatment as usual	BD-I or II; DSM-IV	Mean Age 40.2 (18-64); Female 67%; White 67% BD I 73% BD II 27% N=50	Any current phase; (Actual participant profile: YMRS ≥ 8 , HAM-D ≥ 8 and four or more relapses in past year with 1 event in past 6 months)	Schizoaffective; Other Mental Health Conditions; Pregnant/Nursing
Bowden, 2010 ^{159, 166} Multisite 3 Continents High ROB 20122373 22999893	I: Ziprasidone + Lithium or valproate C: Placebo + Lithium or valproate	BD-I; DSM-IV	Mean Age 38.9 (18+); Female 54%; White 62% N=240	Stabilization after Mania; Initial YMRS ≥ 14 with score ≥ 2 on at least four items at screening and admission. Followed by stabilization: CGI- I ≤ 3 at least 2 consecutive weeks	Substance Abuse; Other Mental Health Condition; Pregnant/Nursing; Labs/Other Conditions
Balance Investigators, 2010 ¹⁶⁰ Multisite 2 Continents Moderate ROB 20092882	I: Lithium + Valproate C1: Lithium C2: Valproate	BD-I; DSM-IV	Mean Age 43 (16+); Female 49%; Race NR N=330	Not having acute episode; Not defined	Pregnant/Nursing

Author, Year Single-/Multisite Location Risk of Bias PMID	Intervention/ Comparison	BD Type; Diagnostic Criteria	Demo- graphics	Current Episode	Key Exclusions
Nierenberg, 2016 ^{157, 158, 177} Multisite US High ROB 26845264 NA 24346608	I: Quetiapine + personalized treatment C: Lithium + personalized treatment	BD-I, II; DSM-IV	Mean Age 39 (18+); Female 59%; White 72% BD I 68% BD II NR N=482	Any current phase	Pregnant/Nursing; Labs/Other Conditions
Vieta, 2010 ¹⁸⁵ Multisite Spain High ROB 20429835	I: Valproate + Aripiprazole C: Lithium + Aripiprazole	BD-I; DSM-IV	Mean Age 43; Female 53%; White 93% N=283	Initial inclusion of manic, partial responders to Lithium or Valproate; Initial YMRS≥16 with decrease of 25% between treatment phases. Patients eligible for this extension if investigator felt the patient would benefit from long- term aripiprazole treatment.	Other Mental Health Conditions; Substance Abuse

BD=bipolar disorder; C=control; CGI-BP=Clinical global impression, bipolar edition; CGI-I=Clinical global impression, global improvement; DSM-IV= Diagnostic and statistical manual, 4th edition; EX=extended release; HAM-D = Hamilton Rating Scale for Depression; I=intervention; MADRS= Montgomery-Asberg depression rating scale; NR=not reported; YMRS=Young mania rating scale.

Combination Drug Therapy for Maintenance Versus Placebo

Thirteen studies examined nine different combination therapies versus placebo in BD-I participants^{88, 116, 163, 166, 174, 175, 179, 182, 183, 186, 188, 189, 192} Four studies also included BD-II participants.^{116, 163, 182, 183} Sample sizes ranged from 25 to 706 and followup lasted from 26 weeks to 2 years.

Evidence was insufficient to address whether nine combinations performed better than placebo: aripiprazole plus mood stabilizers (n=771),^{175, 188} divalproex plus lithium (n=31),¹¹⁶ gabapentin plus mood stabilizers (n=25),¹⁸³ olanzapine plus mood stabilizers (n=99),⁸⁸ oxcarbazepine plus lithium (n=55),¹⁸² perphenazine plus mood stabilizers (n=37),¹⁸⁹ quetiapine plus mood stabilizers (n=1329), long-acting injectable risperidone plus mood stabilizers (n=174),^{163, 174} and ziprasidone plus mood stabilizers (n=240).¹⁶⁶ Single studies, high study limitations, small sample sizes, and imprecision contributed to the insufficient strength of evidence rating. Results were mixed across the studies and generally showed no differences between groups in withdrawals due to adverse events. Serious adverse events were also not different between groups.

Combination Therapy for Maintenance Versus Active Control

Three studies examined combination therapies versus active comparators in BD-I participants, each a unique, single study comparison.^{160, 177, 185} Only one study also enrolled

participants with other types of BD.¹⁷⁷ Sample sizes ranged from 283 to 482 and followup lasted from 24 weeks to 2 years.

Evidence was insufficient to address whether lithium plus valproate performed better than either lithium or valproate alone (n=330),¹⁶⁰ quetiapine plus mood stabilizers performed better than lithium plus another mood stabilizer (n=482),¹⁷⁷ or if aripiprazole plus valproate performed differently than aripiprazole plus lithium (n=283),¹⁸⁵ generally due to high study limitations and imprecision. Overall, the trials reported no significant differences between groups. However, the three-group Balance study reported time to relapse hazard ratios favored lithium plus valproate over valproate alone, but did not significantly differ from lithium alone. Also, serious adverse events did not generally differ between groups. All studies reported at least one death, but not to significant differences between groups for such a rare outcome.

Interpreting the Findings for Drug Treatment for Maintenance

The current evidence for drug treatment for maintenance in BD is largely insufficient to draw conclusions for a number of reasons. First, 36 unique maintenance studies examined 16 different medications often resulting in a single study for a specific comparison for a specific followup duration. In addition, 22 of 36 of maintenance studies (61%) were rated as having severe study limitations (high risk of bias). Second, the high rates of attrition often led to only one usable outcome measure—time to recurrence of a bipolar episode—since this metric accounted for high attrition rates by including information from participants who dropped out due to BD episode relapse. Moreover, 17 studies had small sample sizes of less than 200 participants and 24 studies (66%) had followup between six to twelve months, precluding conclusions for long-term maintenance for most of examined treatments. Third, differences in current bipolar phase criteria across studies, ranging from any current phase (i.e., depression, hypomania, or euthymia), remission from mania, remission from any BD episode, or response or partial response to a specific acute episode treatment, made it difficult to determine for whom findings might apply.

Still, low-strength evidence showed a longer time to recurrence of any BD episode for lithium versus placebo treatment in adults with BD I during a two year followup. The evidence was insufficient for time to recurrence of depression or mania due to inconsistent findings. There was a greater rate of tremors but insufficient evidence for differences in other adverse events rates between lithium versus placebo treatment. In general, in single drug versus placebo comparisons, when reported, placebo showed less tremor than divalproex treatment and less parkinsonism signs than olanzapine treatment, but no differences in other serious adverse events. Also, comparisons between drugs and active comparators did not show differences in serious adverse events, except for less akathisia for divalproex than lithium treatment.

The nature of inclusion criteria and study populations limits the applicability of these findings for certain subpopulations of individuals with BD, such as individuals with BD II, older adults with any BD illness type, and individuals at the early stage of BD illness. For example, 20 studies included individuals with BD I only, while studies with multiple BD disorder subtypes did not report results separately by illness type. The majority of studies included younger adults with mean ages in 30s and early 40s. An additional eight studies excluded individuals experiencing first manic episode. Only two small studies looked at individuals with rapid cycling BD. Most studies did not examine whether the number of prior manic or depressive episodes affected the efficacy of drugs during maintenance phase treatment.

Chapter 7. Psychosocial and Other Nondrug Treatments

Key Points

- Evidence was largely insufficient to draw conclusions regarding the effect of psychosocial interventions compared with either inactive or active comparators for bipolar disorders (BD) for the primary outcomes of interest (relapse, symptom scores, and function). This included the effect of interventions at specific phases (e.g., acute hypomania/mania or depression).
- Low-strength evidence showed no effect of cognitive behavioral therapy (CBT) on depression or mania symptoms when compared with an active comparator.
- Low-strength evidence showed no effect of systematic/collaborative care on relapse rates when compared with an inactive comparator.
- Evidence was insufficient for all other outcomes across all interventions.
- Evidence was insufficient to evaluate other nondrug interventions.

Eligible Studies for Psychosocial and Other Nondrug Treatments

We identified 63 eligible publications that reported 48 unique studies (50 unique comparisons) on psychosocial interventions for BD. We identified one eligible publication on somatic therapy. We excluded six studies during the screening process due to an attrition rate greater than 50 percent.

We analyzed the effect of interventions by category and grouped studies based on whether they used an inactive (i.e., usual care) or active comparator. Included studies on psychosocial therapy examined varied interventions ranging from psychoeducation, CBT, systematic or collaborative care, family or partner interventions (FPI), to interpersonal and social rhythm therapy (IPSRT). The one publication on somatic therapy examined repetitive transcranial magnetic stimulation (rTMS). Results are grouped by general outcome category: relapse, symptom scores (i.e., depression and mania symptoms), function, and additional outcomes (e.g., hospitalizations, suicide rates). None of the included studies reported harms, outside of limited information on self-harm and deaths reported by three studies. For the majority of included studies, the outcome reporting timepoints (6 months and beyond) represent the duration of the treatment and a followup period. For clarity, population/inclusion criteria tables include the number of sessions for psychosocial interventions and the length of time for the intervention (e.g., participants received 12 weekly sessions).

We did not aggregate or pool studies within intervention categories due to differences across studies in inclusion criteria, active components (e.g., individual, group, or internet-based therapy modality), scales used for outcome assessment, and outcome time points. Thus the majority of intervention/ comparator/outcome comparisons were based on single studies. [Appendices J-P](#) provide evidence tables, summary risk of bias assessments, assessments of strength of evidence for key comparisons and outcomes, and reporting for additional outcomes. We calculated effect size (Cohen's d) for individual studies in the appendix tables when sufficient data was available. Table 32 provides a matrix of nondrug interventions and comparators included in the review.

Table 32. Interventions, comparators, and outcomes for nondrug interventions

Intervention Type	Studies	Low or Moderate ROB*	High ROB*	Relapse	Symptom Scores	Function	Additional Outcomes
Psychoeducation vs. Inactive Control	10	6	4	7	5	4	6
Psychoeducation vs. Active Control	3	2	1	2	2	1	1
CBT vs. Inactive Control	8	6	2	7	7	3	4
CBT vs. Active Control	5	5	0	3	5	2	0
Systematic/Collaborative Care vs. Inactive Control	6	6	0	2	5	4	3
Systematic/Collaborative Care vs. Active Control	0	NA	NA	NA	NA	NA	NA
FPI vs. Inactive Control	2	1	1	2	1	0	2
FPI vs.. Active Control	4	4	0	2	3	1	1
IPSRT Inactive Control	1	0	1	1	1	1	1
IPSRT vs. Active Control	1	1	0	0	1	1	1
Combination Interventions vs. Inactive Control	3	3	0	1	3	1	2
Combination Interventions vs. Active Control	2	1	1	1	2	1	1
Other Psychosocial Interventions	3	2	1	1	3	2	0
Somatic Therapy	1	1	0	1	0	0	0
TOTAL	49	35	9	26	36	20	20

*Studies with multiple ROB ratings due to differences in reporting by outcome or across publications are categorized by their average ROB rating

CBT=Cognitive Behavioral Therapy; FPI=Family or Partner Interventions; IPSRT= Interpersonal and Social Rhythm Therapy; ROB=Risk of Bias

Psychoeducation

We identified 14 publications reporting 13 unique studies on psychoeducation as a treatment for BD.¹⁹⁷⁻²¹¹ [Appendix J](#) provides details. We were unable to draw conclusions for psychoeducation interventions due to insufficient evidence.

Psychoeducation Versus Inactive Control

We identified 11 publications reporting 10 unique studies comparing psychoeducation interventions to inactive comparators.^{197-201, 203-208} Six studies were rated low or moderate risk of bias^{198-200, 205, 206 197, 204} while four were rated high.^{201, 203, 207, 208} Study sample size ranged from 50 to 233. The majority of studies enrolled patients who were euthymic. Components of the psychoeducation included discussions about symptoms, medications, and relapse prevention. Formats for interventions included individual, group, and internet-based psychoeducation. Inactive comparisons included treatment as usual (including pharmacotherapy) and attention controls.

Table 33 provides a summary of inclusion/exclusion criteria and interventions and comparators. [Appendix J](#) provides details.

Table 33. Population and inclusion criteria for studies of psychoeducation versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Barnes, 2015 ¹⁹⁷ Singlesite Australia Moderate ROB 25554993	Internet-based psychoeducation (Road to Recovery for Bipolar Disorder) focused on managing symptoms, medication, psychological approaches, relationships, and lifestyle. Participants had access to 10 sessions of cognitive behavioral therapy as homework -20 online sessions, first 8 sessions weekly, 9 and 10 every 2-week period, and 11-20 were monthly	Internet-based attention control (Virtual Highway for Bipolar Disorder) -20 online sessions, first 8 sessions weekly, 9 and 10 every 2-week period, and 11-20 were monthly	BD-I or II; DSM-IV No current clinical state excluded. Severe episodes not reported.	Mean Age 40 (18-58) 72% Female Race NR N = 233	Labs/Other Medical Conditions
Gumus, 2015 ²⁰⁸ Singlesite Turkey High ROB 26001717	Psychoeducation focused on illness education, warning signs, medication and side effects, and problem solving skills as well as standard clinical monitoring - 60 minute sessions, once per week, for 4 weeks	Standard clinical follow up (not described) -Duration of study	BD-I or II; DSM-IV Euthymic/Maintenance	Mean Age 39 (27-52) Female 48% Race NR N=82	Other Mental Health
de Barros Pellegrinelli, 2013 ²⁰¹ Singlesite Brazil High ROB 22943487	Psychoeducation consisting of 15 min introduction, 30 min education, 30 min discussion and psychological support, and 15 min for conclusion -16 twice-weekly 90-minute sessions	Sessions promoting relaxation consisting of informal conversation and relaxation using three different types of exercises -16 twice-weekly 90-minute sessions	BD-I or II; DSM-IV Euthymic/Maintenance	Mean Age 44 (22-66) 69% Female Race NR N=55	Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Javadpour, 2013 ²⁰³ Singlesite Iran High ROB 23642977	Psychoeducation focusing on understanding bipolar, familiarization with symptoms understanding signs of an episodes, awareness of causes and prognosis, education about the function, types and adverse side effect of mood stabilizer medication, functions, types and adverse effects of anti-manic and antidepressant medications, and risks of discontinuing medications - Eight 50-minute weekly session	Standard pharmacotherapy (discretion of treating psychiatrist of their choice)	BD type not specified Euthymic/Maintenance	Mean Age NR (18-60) 51% Female Race NR N = 108	First Manic Episode
Smith, 2011 ²⁰⁶ Singlesite United Kingdom Low ROB 22017225	Internet-based psychoeducation focusing on causes, role of medication, lifestyle changes, relapse prevention and early intervention, psychological approaches, gender-specific considerations, and advice for family and careers - Initial face-to-face meeting with psychiatrist to learn how to use program followed by four months of every-other-week online psychoeducation	Treatment as usual: Usual care delivered in a collaborative model between general practitioners and community mental health teams.	BD-I, II or NOS; DSM-IV Euthymic/Maintenance	Mean Age 44 (22-66) 62% Female 98% White N = 50	Neurological Disorders
Colom, 2009 ²⁰⁰ Colom, 2003 ¹⁹⁸ Singlesite Spain Low ROB 12695318 19252157	Group psychoeducation (and pharmacologic treatment) that focused on illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and life-style regularity -21 weekly 90-minute sessions	Standard pharmacologic treatment and group meetings with psychologists without any psychosocial feedback (unless necessary for patient interaction) -20 weekly group sessions	BD-I or II; DSM-IV Euthymic/Maintenance	Mean Age NR (18-65) 63% Female Race NR N = 120	Other Mental Health; Neurological Disorders

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Sajatovic, 2009 ²⁰⁵ Singlesite United States Low ROB 19723732	Group psychoeducation (Life Goals Program) focusing on illness education, medication adherence, management, goal setting, and problem solving -6 weekly sessions followed by optional monthly group sessions	Treatment as usual: Treatment at community mental health care including medication management and psychosocial therapy and counseling	BD-I or II; DSM-IV No current clinical state excluded. Severe episodes not reported.	Mean Age 41 (18-76) 68% Female 60% White N = 164	Other Conditions
Colom, 2003b ¹⁹⁹ Singlesite Spain Low ROB 14628987	Group psychoeducation (and standard treatment) focused on illness awareness, treatment compliance, prodromal symptoms and relapse, lifestyle regularity, symptom monitoring, treatment adherence, and illness management skills. -20 weekly group sessions for 90 minutes	Standard pharmacologic treatment and group meetings with psychologists without any psychosocial feedback (unless necessary for patient interaction). Therapists encouraged communication between patients. -20 weekly group sessions	BD-I; DSM-IV Euthymic/Maintenance	Mean Age 35 (18-57) 72% Female N = 50	Other Mental Health; Neurological Disorders; Taking Other Meds
Weiss, 2000 ²⁰⁷ Singlesite United States High ROB 10847311	Psychoeducation focused on acceptance, self-help, identifying and fighting triggers, medication adherence, coping skills, and similarities between recovery and relapse for bipolar and substance abuse -12-20 weekly group therapy, 60 minutes per session	Treatment as usual/No treatment (not described) with 6 monthly assessments	BD-I, II, or NOS; DSM-IV No current clinical state excluded. Severe episodes not reported.	Mean Age 36 (18-54) 49% Female 87% White N = 45	Neurological Disorders; Other Conditions (which would preclude attendance)

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Perry, 1999 ²⁰⁴ Multisite United Kingdom Moderate ROB 9888904	Psychoeducation (and routine treatment) involving 12 individual treatment sessions that focused on identifying prodromal symptoms and producing and rehearsing an action plan once prodromes had been recognized	Treatment as usual: Drug treatment, monitoring of mood and adherence to treatment, education about BD, and inpatient care if necessary.	BD Type Not Specified Maintenance	Mean Age 45 (23-67) 68% Female 91% White N = 69	Substance Abuse; Neurological Disorders

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; NOS= not otherwise specified; N=number; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of psychoeducation on relapse when compared with an inactive comparator due to moderate study limitations, inconsistent findings, and imprecision. Seven studies enrolling 712 participants reported information on relapses.^{203, 204, 206 197-200} Reported results regarding the number of relapses were mixed across studies rated low or moderate risk of bias. Two studies reported that participants who had received psychoeducation had fewer relapses of any type at 2 years than those who received an inactive comparator.¹⁹⁸⁻²⁰⁰ Colom et al. also reported fewer relapses of any type for those that received psychoeducation at 5 years.²⁰⁰ However, Perry et al. (n=69) reported significance differences only for manic relapses at both 6 and 18 months, with fewer manic relapses in the psychoeducation group. Groups did not differ for depressive relapses at either outcome time point.²⁰⁴ Smith et al. (n=50) reported no difference between groups in the number of depressive or manic relapses at 10 months.²⁰⁶ Barnes et al. reported no difference in recurrence at 12 months.¹⁹⁷ The study also reported no difference between groups in time to recurrence.¹⁹⁷

Results were also mixed for studies rated high risk of bias. Javadpour et al. (n=108) reported fewer recurrences in the psychoeducation group at 18 months.²⁰³ However, Gumus (n=82) reported no difference between groups in relapses at 12 months.²⁰⁸

Symptom Scores

Evidence was insufficient for depression and mania symptoms due to high study limitations and imprecision. Five studies enrolling 422 participants reported measures of symptom scores.^{201, 203, 205-207} All five studies, including three rated high risk of bias, reported no difference between groups in depression symptoms across a range of outcome time points (6 to 18 months).^{201, 203, 205-207}

Two low risk of bias studies reported no difference between groups in mania symptoms (at 6 or 12 months).^{205, 206} The two high risk of bias studies also reported no difference between groups.^{201, 203} Rated high risk of bias, Weiss et al. (n=45) reported statistically significant improvements in mania at 6 months for participants receiving psychoeducation group compared with the control group.²⁰⁷

Function

Evidence was insufficient for psychoeducation on all function outcomes due to moderate study limitations and strong imprecision. Four studies enrolling 446 participants reported measures of function.^{201, 204-206} For global function, Sajatovic et al. (n=164) and Smith et al. (n=50) found no difference between groups at their respective outcome time points (6 to 12 months).^{205, 206} Rated high risk of bias, de Barros Pellegrinelli et al (n=55) also found no difference between groups at 12 months.²⁰¹

Results for other measures of function were mixed. One low risk of bias study reported no difference between groups in measures of quality of life.²⁰⁶ One moderate risk of bias study found no difference between groups in social function at 6 months; however, at 18 months there was a better function in the intervention group.²⁰⁴

Additional Outcomes

Six studies reported data on hospitalizations.^{197-200, 203, 207, 208} Four studies, including two rated high risk of bias, reported no difference between groups in number of hospitalizations across a range of time periods (12 months to 5 years).^{197, 198, 200, 207, 208} One low risk of bias study

reported fewer hospitalizations for those who received psychoeducation at 2 years.^{197, 199} Rated high risk of bias, Javadpour et al. (n=108) reported fewer hospitalizations for those who received psychoeducation at 18 months.²⁰³

Psychoeducation Versus Active Control

We identified three studies on the effect of psychoeducation interventions compared with active comparators.²⁰⁹⁻²¹¹ Two studies were rated moderate risk of bias,^{209, 211} and one was rated high.²¹⁰ Study sample size ranged from 85 to 304. The majority of studies enrolled patients who were euthymic and used a group format for the intervention. Components of the psychoeducation included discussions about illness symptoms, medications, and recognition of early warning signs. Two studies examined the effect of different formats of psychoeducation (i.e., group vs. individual, guided vs. self-administered).^{209, 210}

Table 34 provides a summary of inclusion/exclusion criteria and interventions and comparators. [Appendix J](#) provides details.

Table 34. Population and inclusion criteria for studies of psychoeducation versus active comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Bilderbeck, 2016 ²⁰⁹ United Kingdom Singlesite Moderate ROB 27454410	Therapist facilitated psychoeducation via manual focused on identifying the relapse, reviewing risk factors, daily sleep regulation, medications and substance abuse; and mood management planning. -5 face to face sessions over 12 weeks	Self-administered psychoeducation via manual focused on identifying the relapse, reviewing risk factors, daily sleep regulation, medications and substance abuse; and mood management planning. -Manual access for 12 weeks	BD I or II; DSM-IV Euthymic/Maintenance	Mean Age 44 (16-76) Female 73% White 93% N =121	Labs/Other Conditions
Kallestad, 2016 ²¹⁰ Singlesite Norway High ROB 27253214	Group psychoeducation focused on illness education, symptoms, early detection, sleep, risk factors, stress management, causes, work, social rights/welfare system and law/regulations -Ten initial 90-minute sessions and 8 booster sessions over next 2 years at 3-month intervals	Individual psychoeducation focused on treatment, stress management, sleep, dysfunctional cognitions, and other psychosocial factors associated with increased risk of relapse -Three 1-hour weekly sessions	BD I or II; DSM-IV No current clinical state excluded	Mean Age 38 (19-64) Female 54% Race NR N = 85	Labs/Other Conditions; Neurological Disorders
Morriss, 2016 ²¹² Multisite United Kingdom Moderate ROB 27688021	Structured group psychoeducation focused on life charting, recognition of early warning signs, problem solving, sleep hygiene, and care planning -21 weekly sessions for 2 hours each over a maximum of 26 weeks.	Optimized unstructured group support where participants set the agenda at each meeting -21 weekly sessions for 2 hours each over a maximum of 26 weeks	BD I or II; DSM-IV Euthymic/Maintenance	Mean Age 45 (33-57) Female 58% Race NR N = 304	Labs/Other Conditions; Other Mental Health

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; NOS= not otherwise specified; N=number; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient on the effect of psychoeducation on relapse compared with an active comparator, due to moderate study limitations and strong imprecision. Two moderate risk of bias studies enrolling 425 participants reported information on relapses.^{209, 211, 212} One study compares psychoeducation formats.²⁰⁹ Both studies reported no difference between the psychoeducation interventions and active comparators in number of relapses.^{212 209, 211} Morriss et al. (n=121) also reported time to relapse, finding no difference between groups over 96 weeks.^{211, 212}

Symptom Scores

Evidence was insufficient on the effect of psychoeducation on relapse compared with an active comparator, due to moderate study limitations and strong imprecision. Two moderate risk of bias studies enrolling 425 participants reported information on symptom scores.^{209, 212} One study compares psychoeducation formats.²⁰⁹ Both studies reported no difference between the psychoeducation interventions and active comparators in depression and mania symptoms.^{209, 212}

Function

Evidence was insufficient on the effect of psychoeducation on function compared with an active comparator due to high study limitations, unclear consistency, and imprecision. No studies reported measures of global function. One moderate risk of bias study enrolling 121 participants reported information on other measures of function.²⁰⁹ The study reported no difference between psychoeducation and the active comparator in social and occupational function at 96 weeks.²⁰⁹

Additional Outcomes

Two studies reported hospitalizations.^{209, 210} Rated moderate risk of bias, Bilderbeck et al. (n=121) found no difference between groups in hospitalizations at 12 months, but this study's active comparator was another format of psychoeducation (i.e., self-administered via a manual). Rated high risk of bias, Kallestad et al. (n=85) reported that individuals who received group psychoeducation had a longer time to first hospital admission compared to individuals who received individual psychoeducation.²¹⁰

Cognitive Behavioral Therapy

We identified 14 publications reporting 13 unique studies on CBT as a treatment for BD.²¹³⁻²²⁶ [Appendix K](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes. A summary of findings with at least low-strength evidence for other drug treatments for maintenance are provided in Table 35. Any intervention and comparison not listed in Table 35, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 35. Summary of findings with at least low-strength evidence for cognitive behavioral therapy

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
CBT vs. Active Comparators*	5 RCTs ^{213, 214, 219, 215, 210, 221} (n=461) 6 to 12 months	Depression and Mania symptoms: No difference between groups across range of time periods.	Low (moderate study limitations, imprecision)

* Active comparators are comparators such as a different psychosocial therapy or peer support.

CBT=cognitive behavioral therapy; n=number; RCT=randomized controlled trial

Cognitive Behavioral Therapy Versus Inactive Control

We identified nine publications reporting eight unique studies on the effect of CBT when compared with an inactive comparator yielding insufficient evidence for various outcomes.^{215, 218-220, 222-226}

One study was rated low to high risk of bias due to differences in reporting of outcomes: low for pre-specified outcomes.²¹⁵ Two studies were rated high risk of bias.^{222, 225} Study sample sizes ranged from 52 to 253. The majority of studies enrolled patients without a current bipolar episode, while some did not exclude individuals based on the current clinical state except for acute mania. Components of the CBT interventions varied (e.g., group vs. individual; 8 vs. 20+ sessions); however, common elements included education about BD, identifying symptoms, and discussing strategies for management and coping. The length of interventions also varied ranging from 8 weeks to 6 months. Inactive comparisons were generally defined as “treatment as usual”, which generally involved medication and variable contact with a provider. Five studies were rated low or moderate risk of bias.^{218-220, 223, 224, 226}

Table 36 summarizes the key characteristics of the studies. [Appendix K](#) provides details.

Table 36. Population and inclusion criteria for studies of CBT versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Jones, 2015 ²²⁰ Multisite United Kingdom Moderate ROB 25213157	Individual CBT focused on recovery approach, mood functioning, understanding of diagnosis, recovery-informed goals, relationships between mood and progress towards recovery goals, CBT techniques to cope, functioning issues in relation to recovery, development of recovery plan, and sharing lessons from therapy with stakeholders -Total of 18 hours over 6 months; weekly or biweekly 45-60 minute sessions	Treatment as usual: Routine medication (mood stabilizers, antipsychotics, and antidepressants) and medical care from clinician and community mental health team.	BD-I and BD-II; DSM-IV Euthymic/Maintenance	Mean Age 39 (18-65) 70% Female 96% White N = 67	Schizoaffective
Perich, 2013 ²²⁶ Singlesite Australia Moderate ROB 23216045	Group mindfulness-based CBT consisting of mindfulness meditation practice and cognitive therapy regarding depression including psychoeducation (education about BD, depression, hypo/mania, and anxiety). -8 weekly sessions, each 2 to 2.5 hours	Treatment as usual: Weekly handouts with information about BD via email or mail. Topics included causes of BD, available treatments, and common symptoms.	BD-I and BD-II; DSM-IV Euthymic/Maintenance	Mean Age NR (18+) 65% Female Race NR N = 95	Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Labs/Other Conditions
Fava, 2011 ²²³ Singlesite Italy Low ROB 21372621	CBT and well-being therapy focused on patient's symptomatology, monitoring of distress, strategies for symptom management, psychotherapeutic strategy for enhancing well-being -10 sessions every other week for 45-minutes.	Clinical Management: Reviewed the patient's clinical status and provided the patient with support and advice according to protocol -10 sessions every other week for 45-minutes.	Cyclothymic; DSM-IV No history of mania or major depressive disorder	Mean Age 40 (18-65) 55% Female Race NR N = 62	First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Medications; Pregnant/Nursing; Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Gomes, 2011 ²²² Singlesite Brazil High ROB 21372622	Group CBT focused on information about BD and stabilized routine and pharmacological issues; use of mood graphs and stress vulnerability model, cognitive and behavioral strategies to manage depressive and manic episodes; specific problems in BD; techniques to improve relapse prevention -18 structured sessions, 90 minutes each	Treatment as usual: Pharmacological treatment	BD-I and BD-II; DSM-IV Euthymic/Maintenance	Mean Age 39 (18-60) 76% Female Race NR N = 50	Substance Abuse; Neurological Disorders
Castle, 2010 ²²⁴ Multisite Australia Low ROB 20435965	Group CBT focused on monitoring mood and activities, assessing prodromes, preventing relapse, and setting specific, measurable, achievable, realistic, time-framed goals -12 weekly group sessions (90 minutes) and 3 monthly booster sessions with weekly telephone calls	Treatment as usual (not defined) and weekly telephone calls	BD-I, BD-II, BD NOS DSM-IV-TR Euthymic/Maintenance	Mean Age 42 (18-65) 76% Female Race NR N = 84	Schizoaffective; Neurological Disorders; Labs/Other Conditions
Ball, 2006 ²²⁵ Singlesite Australia High ROB 16566624	CBT focused on assessment, psychoeducation, identifying early warning signs, establishing stable routines, identifying and modifying cognitions, identifying and modifying schemas -20 weekly sessions, 60 minutes each	Treatment as usual: Regular sessions as prescribed by patient's medical practitioner	BD-I and BD-II; DSM-IV Without a current episode of severe depression or mania	Mean Age 42 (23-77) 58% Female Race NR N = 52	Schizoaffective; Other Mental Health; Neurological Disorders; Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Scott, 2006 ²¹⁵ Singlesite United Kingdom Low/High ROB (by outcome) 16582056	CBT focused on facilitating acceptance of the need for treatment, reducing variability in mood, managing stressors, strategies to cope with depression, identifying and modifying dysfunctional automatic thoughts and beliefs, improve medication adherence, tackling substance misuse, teaching early recognition of symptoms of recurrence and coping techniques for symptoms -Weekly sessions for 15 weeks with reduction in frequency from week 16- 26. Two booster sessions at week 32 and 38.	Treatment as usual: Medication and contact with key mental health professionals when appropriate.	BD-I and BD-II DSM-IV Any Episode (25% depressed, 10% hypo/manic, remaining without current episode)	Mean Age 41 (18- 65) 65% Female Race NR N = 253	First Manic Episode; Substance Abuse; Other Mental Health; Neurological Disorders
Lam, 2003 ²¹⁸ , 2005 ²¹⁹ Singlesite United Kingdom Moderate ROB 12578431 15677598	CBT focused on traditional cognitive therapy for depression, diathesis-stress model and need for pharmaceutical and psychological therapy, mood monitoring and prodromes, sleep importance, and targeting extreme striving attitudes and behavior -12 to 18 individual 60-minute sessions in the first 6 months and 2 booster sessions in the second 6 months.	Minimal psychiatric care: Mood stabilizers (at appropriate level) and regular outpatient psychiatric follow up	BD-I; DSM-IV Euthymic/Maintenanc e	Mean Age 44 (22- 70) 56% Female Race NR N = 103	First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health

BD=Bipolar Disorder; CBT=cognitive behavioral therapy; DSM= Diagnostic and Statistical Manual of Mental Disorders; NOS=Not otherwise specified; N=number; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of CBT interventions on relapse when compared with an inactive comparator, due to moderate study limitations, inconsistent findings, and imprecision. Seven studies enrolling 714 participants reported number of relapses.^{215, 218-220, 224, 226 225 222} Among the studies rated low or moderate risk of bias, two studies reported that individuals who received CBT had significantly fewer relapses of any type compared to those that received an inactive comparator.^{218, 219, 224} However, three studies showed no difference between groups in number of relapses.^{215, 220, 226} Jones et al. and reported longer times to recurrence for individuals who received CBT interventions.²¹⁵

Two high risk of bias studies reported no difference between groups in number of relapses.^{225 222} Gomes et al. reported longer times to recurrence for individuals who received CBT interventions.²²²

Symptom Scores

Evidence was insufficient for the effect of CBT interventions on depression and mania symptoms when compared with an inactive comparator, due to moderate study limitations, inconsistent findings, and imprecision. Seven studies enrolling 716 participants provided information on symptom scores.^{223 218, 219, 224, 220, 215, 226, 225} Results for depression symptoms were mixed for studies rated low or moderate risk of bias. Fava et al. (n=62) reported statistically significant improvements in depression for the CBT intervention group compared with an inactive comparator.²²³ Five studies found no difference between groups in depression at any time point.^{218, 219, 224, 220, 215, 226} Rated high risk of bias, Ball et al. (n=52) reported a significant difference between groups in depression at 6 months. However, at 18 months there was no difference between groups.²²⁵

Similarly, evidence for mania symptoms was inconsistent among studies rated low or moderate risk of bias. Fava et al. (n=62) reported statistically significant improvements in mania for the CBT intervention group compared with an inactive comparator.²²³ Lam et al. (n=103) found no difference between groups at nearly all reported time points (6, 12, 18, and 24 months) with exception of final time point at 30 months, when an improvement was seen for the intervention group, although this finding may not have been corrected for multiple outcome tests.^{218, 219} Four studies found no difference between groups in mania at any time point.^{215, 220, 224, 226} Rated high risk of bias, Ball et al. found no difference between groups in mania at any time point.²²⁵

Function

Evidence was insufficient for the effect of CBT interventions on all measures of function when compared with an inactive comparator due to moderate study limitations, unclear or inconsistent findings, and imprecision. Three studies enrolling 280 participants reported outcomes on function.^{218-220, 225} Rated high risk of bias, only Ball et al. (n=52) assessed global function, finding no difference between groups at 6 and 18 months.²²⁵

Two moderate risk of bias studies reported other measures of function. Lam et al. (n=103) measured social function, finding no difference between groups at nearly all outcome time points (12, 18, and 30 months), with the exception of 6 and 24 months, when a significant difference favored the intervention (which may not have been adjusted for multiple outcome tests).^{218, 219} Jones et al. (n=67) measured both social function and quality of life, finding no difference between groups at 6 or 12 months.²²⁰ In addition, one high risk of bias study reported one

measure of social function, cognitive function, and health and disability. The measure of health and disability showed a significant difference favoring the intervention at 6 months, but not at 18 months. There were no differences between groups for either time point for the other two measures.²²⁵

Additional Outcomes

One high risk of bias study reported information on hospitalizations. Lam et al. (n=103) found that significantly more individuals in the control group were admitted for bipolar episodes compared to those who received CBT.²¹⁸

Cognitive Behavioral Therapy Versus Active Control

We identified five unique studies enrolling a total of 461 participants examining the effect of CBT compared with active comparators.^{213, 214, 216, 217, 221} All five publications were rated as low or moderate risk of bias.^{213, 214, 216, 217, 221} The total sample sizes ranged from 58 to 204 participants. Populations across the studies varied; however the majority enrolled participants without a current bipolar episode. Components of the CBT interventions also varied; however, common elements included education about BD and relapse prevention. Active comparisons ranged from supportive therapy, group drug counseling, and psychoeducation

Table 37 summarizes the key characteristics of the studies. [Appendix K](#) provides details.

Table 37. Population and inclusion criteria for studies of CBT versus active comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Harvey, 2015 ²²¹ Singlesite United States Moderate ROB 25622197	CBT for insomnia focusing on stimulus control, bed and sleep associations, regularizing sleep and wake times, sleep/circadian education, relaxing wind down, sleep-enhancing activities, and devising a wake-up routine. The module altered unhelpful beliefs about sleep, bedtime worry, rumination, and vigilance -8 weekly 50-60 minute sessions with behavioral module	Psychoeducation sessions that provided information but no facilitation or plan for behavior change. Sessions focused on mood regulation, the etiology of bipolar disorders, symptoms, prodromes, medications, substance use, diet, physical activity, stress management, relaxation, and self-esteem and sleep in a social context -8 weekly 50-60 minute sessions	BD-I ; DSM-IV-TR No current bipolar episode (interepisode)	Mean Age 37 (18-62) 62% Female 64% White N = 58	Substance Abuse; Other Mental Health; Neurological Disorders; Pregnant/Nursing; Labs/Other Conditions
Meyer, 2012 ²¹⁷ Singlesite Germany Low ROB 22099722	CBT focused on understanding of BD, identifying early warning symptoms, strategies for management, communication and problem solving skills -20 sessions over 9 months, 50-60 minutes each	Supportive Therapy: Client-centered focus; whatever problems the patient presented were dealt with by providing emotional support and general advice -20 sessions over 9 months, 50-60 minutes each.	BD-I and BD-II; DSM-IV Euthymic/Maintenance	Mean Age 44 (18-75) 50% Female Race NR N = 76	Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Medications

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Parikh, 2012 ²¹⁶ Multisite Canada Low ROB 22795205	CBT including psychoeducation, understanding of personal warning signs for onset and action plan, and cognitive restructuring of dysfunctional thoughts and assumptions -20 individual 50-minute sessions	Group psychoeducation using Life Goals manual; focused on illness recognition, treatment approaches, and coping strategies and the creation of Personal Care Plan including action plan for both depression and mania -6 sessions, 90 minutes each session	BD-I and BD-II DSM-IV Euthymic/Maintenance	Mean Age 40.9 (18-64) 58% Female Race NR N = 204	First Manic Episode; Substance Abuse; Other Mental Health; Neurological Disorders; Labs/Other Conditions
Weiss, 2009 ²¹⁴ Singlesite United States Low ROB 19573999	Integrated group CBT on the cognitive-behavioral relapse prevention model which focuses on the similarities between recovery and relapse processes in BD and substance abuse and their interaction -12 weekly 60-minute sessions	Group Drug Therapy: Substance use disorders therapy sessions that focused on facilitating abstinence, encouraging mutual support, and teaching new ways to cope with substance-related problems -12 weekly 60-minute sessions	BD-I, BD-II, and BD NOS DSM-IV Non-manic	Mean Age 38 (18-58) 41% Female 92% White N = 61	First Manic Episode; Schizoaffective; Other Mental Health; Labs/Other Conditions
Weiss 2007 ²¹³ Singlesite United States Moderate ROB 17202550	Integrated group CBT on cognitive-behavioral relapse prevention model which focuses on the similarities between recovery and relapse processes in BD and substance abuse and their interaction -20 weekly 60-minute sessions	Group Drug Therapy: Focused on facilitating abstinence, encouraging mutual support, and teaching new ways to cope with substance-related problems -20 weekly 60-minute sessions	BD-I, BD-II, and BD NOS; DSM-IV Maintenance	Mean Age 41.9 (22-65) 52% Female 94% White N = 62	First Manic Episode; Schizoaffective; Other Mental Health; Labs/Other Conditions

BD=Bipolar Disorder; CBT=cognitive behavioral therapy; DSM= Diagnostic and Statistical Manual of Mental Disorders; N=number; NOS=Not Otherwise Specified; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of CBT on relapse compared with an active comparator, due to moderate study limitations, inconsistent findings, and imprecision. Three low or moderate risk of bias studies enrolling 338 participants reported number of relapses.^{216, 217, 221} Meyer et al. (n=76) reported no difference between groups in recurrence of any type of effective episode at both 9 and 30 months. Consistent with these findings, Parikh et al. (n=204) found no difference in the number of manic or depressive relapses over 72 weeks. Harvey et al. (n=58) found that while individuals who received CBT had fewer hypomanic/manic relapses than those who received psychoeducational therapy, there was no difference between groups in depressive relapses.

Symptom Scores

Low-strength evidence (moderate study limitations, imprecision) showed no effect of CBT on depression or mania symptoms when compared to an active comparator. Five low or moderate risk of bias studies enrolling 461 participants provided information on symptom scores.^{213, 214, 216, 217, 221} All five included studies reported no difference between groups in depression or mania symptoms across a range of outcome timepoints.^{213, 214, 216, 217, 221}

Function

Evidence was insufficient for all measures of function due to unclear consistency and strong imprecision. Two studies enrolling 134 participants reported outcomes for function.^{217, 221} Rated low risk of bias, Meyer et al. (n=76) reported a measure of global function, finding no difference between groups. Rated moderate risk of bias, Harvey et al. (n=58) reported one measure of quality of life and one measure of disability. At 6-months of followup, groups did not differ for either measure.

Systematic or Collaborative Care

We identified eight publications reporting six unique studies on systematic or collaborative care for BD.²²⁷⁻²³⁴ [Appendix L](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes. A summary of findings with at least low-strength evidence for other drug treatments for maintenance are provided in Table 38. Any intervention and comparison not listed in Table 38, or outcome not listed for an included intervention and comparison, was found to have an evidence base insufficient to draw conclusions.

Table 38. Summary of findings with at least low-strength evidence for cognitive behavioral therapy

Intervention	# Studies/ Design (n Analyzed) Timing	Findings	Strength of Evidence
Systematic or Collaborative Care vs. Inactive Comparators*	2 RCTs ^{228 232} (n=599) 7 to 12 months	Relapse Rate: No difference between groups across different time periods.	Low (moderate study limitations, imprecision)

*Inactive comparators are comparators such as usual care, no intervention.
n=number; RCT=randomized controlled trial

Systematic or Collaborative Care Versus Inactive Control

We identified eight publications reporting six unique studies on the effect of systematic or collaborative care compared with an inactive comparator. Four studies were rated as low or moderate risk of bias.^{227, 229, 230, 233, 234} Simon et al. was rated low risk of bias for all outcomes except symptom scores where it was rated high risk of bias.^{231, 232} Kessing et al. was rated low risk of bias for the outcome of hospitalizations and high risk of bias for all other reported outcomes.²²⁸ Study sample sizes ranged from 61 to 441. The majority of studies did not exclude individuals based on their current clinical state (e.g., acute depression, acute hypomania, euthymia). Components of the interventions included interaction with a care team and psychoeducation or CBT. Length of the intervention ranged from 6 months to two years. Inactive comparisons were generally defined as “treatment as usual”, which included standard mental health care (including pharmacotherapy) with or without an added component for monitoring.

Table 39 summarizes the key characteristics of the studies. [Appendix L](#) provides details.

Table 39. Population and inclusion criteria for studies of systematic or collaborative care versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
van der Voort, 2015 ²³³ van der Voort, 2015b ²³⁴ Multisite Netherlands Low ROB 25792695 25841077	Collaborative care including formation of care team (including a family member with patient consent), formation of treatment plan with needs assessment, psychoeducation, problem solving treatment, mood charting, recognition of early warning signs and formation of relapse prevention, and pharmacotherapy and somatic care. -12 months of collaborative care	Treatment as usual (not described)	BD-I, II or NOS; DSM-IV Maintenance/Non-Specific (No Severe Episodes)	Mean Age 46 (18-65) 64% Female Race NR N=138	Other Mental Health; Labs/Other Conditions
Kessing, 2013 ²²⁸ Multisite Denmark Low/High ROB (based on outcome) 23349295	Specialized outpatient care including a medical evaluation, treatment plan, pharmacological treatment, group sessions consisting of psychoeducation and discussions about participants experiences and a discharge group focused on identifying early warning signs and communication of signs to clinicians. -Specialized care for 2 years including 12 sessions of psychoeducation (1.5 hours per session) and 3-6 months of discharge group	Treatment as usual: Standard outpatient mental health services included treatment with a general practitioner, psychiatrist, or community mental health center.	Manic Episode or BD-I, II, or NOS; ICD-10 code: DF 30.1-31 Non-specific (Recent hospitalization for episode)	Mean Age 37 (27-48) 54 % Female Race NR N=158	Neurological Disorders; Other Mental Health; Labs/Other Conditions
Kilbourne, 2012 ²²⁹ Multisite US Low ROB 23203358	Life Goals Collaborative Care consisting of weekly group self-management sessions (mixture of motivational interviewing and cognitive behavioral techniques) with care management by interventionist and providers -Four 2-hour sessions of self-management, 6 months of care management	Enhanced treatment as Usual: Usual care and monthly mailings on mental health care and referrals to primary care services	BD-I, II or NOS; NR No current clinical state excluded. Severe episodes not reported.	Mean Age 43 (18-71) 61% Female 78% White N=68	Neurological Disorders; Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Kilbourne, 2008 ²³⁰ Single-site US Moderate ROB 18586993	Bipolar disorders medical care model consisting of self-management (adapted for Life Goals Program) education, care management via nurse care manager who coordinated with providers regarding medical and psychiatric care, and guideline implementation training for providers -Three sessions (2 hours) of self-management program; 6 months of care management	Treatment as usual: Routine care (as selected by provider) without self-management or care management	BD-I, II or NOS; NR No current clinical state excluded. Severe episodes not reported.	Mean Age 55 (39-71) 9% Female 90% White N=61	Substance Abuse; Other Mental Health; Labs/Other Conditions
Bauer, 2006 ²²⁷ Multisite US Low ROB 16816277	Bipolar Disorders Program including psychoeducation via the Life Goals Program and care team consisting of nurse care coordinator and psychiatrist -3 years of care via the program	Treatment as usual: Treatment based on psychiatrist choice	BD-I, II or NOS; DSM-IV No current clinical state excluded. Severe episodes not reported.	Mean Age 47 (26-66) 28% Female 29% White N=330	Neurological Disorders; Labs/Other Conditions
Simon, 2006 ²³¹ Simon, 2005 ²³² Low/High ROB (based on outcome) 15842025 16651507	Systematic care consisting of structured initial assessment and planning, telephone monitoring, coordinated mental health treatment team, and psychoeducation. -Services offered for 24 months post-randomization	Treatment as usual: Services that are normally available without any additional care	BD-I or II; DSM-IV No current clinical state excluded. Severe episodes not reported.	Mean Age 44 (20-68) 68% Female 88% White N=441	Neurological Disorders; Labs/Other Conditions

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; N=number; NOS=Not Otherwise Specified; N=number; NR=not reported; ROB=risk of bias

Relapse

Low-strength evidence (moderate study limitations, imprecision) showed no effect for systematic/collaborative care on relapse. Two studies, one low risk of bias and one high risk of bias, enrolling 599 participants reported number of relapses.^{228, 232} Both studies reported no difference between groups in manic or depressive relapses at the reported outcome time points (1-3 years).^{228, 232}

Symptom Scores

Evidence was insufficient for the effect of systematic/collaborative care on depression and mania symptoms when compared with an inactive comparator due to moderate study limitations, inconsistent findings, and imprecision. Five studies enrolling 1,038 participants reported symptom scores.^{227, 229-234}

Among studies rated low or moderate risk of bias, one study reported no difference between groups in depression symptoms at 6 months.²³⁰ Kilbourne et al. (n=68) reported no difference between groups across 6-12 months.²²⁹ Bauer et al. (n=306) reported no difference between groups in depression at 3 years. However, while van der Voort et al. (n=138) reported no difference between groups at 6 months, there was a statistically significant difference at 12 months, favoring the intervention.²³³ Rated high risk of bias, Simon et al. (n=441) found that there were less depression symptoms in the collaborative care intervention group at 12 months. However, there was no difference between groups across the full 24-month follow-up period.

Four low or moderate risk of bias studies reported no difference between groups in mania symptoms at their respective outcome time points.^{227, 229, 230, 233} Rated high risk of bias, Simon et al. (n=441) reported no difference between group in mania at 12 months, but less mania symptoms in the systematic/collaborative care group across the full 24-month follow-up period.^{231, 232}

Function

Evidence was insufficient for the effect of systematic/collaborative care on global function and other measures of function when compared with an inactive comparator due to unclear or inconsistent findings and strong imprecision. Four studies enrolling 597 participants reported measures of function.^{227, 229, 230, 234}

One low risk of bias study reported a measure of global function. The study reported no difference between groups at 6 months, but better function for those that received the systematic/collaborative care intervention at 12 months.²³⁴ Four low or moderate risk of bias studies reported additional measures of function. No difference was found between groups in quality of life at both 6 and 12 months.²³⁴ Similarly, no difference was found between groups in measures of mental function, physical function, and health and disability at 6 months.^{229, 230} Based on the data from Kilbourne et al. (n=68), no differences occurred between groups in mental function and physical function at 12 months; however there was a difference in health and disability favoring the intervention.²²⁹ Bauer et al. (n=330) found no difference between groups in physical function at 3 years, but reported a significant difference in mental function with better function in those who received the intervention.²²⁷

Additional Outcomes

Two low risk of bias studies reported additional outcomes related to hospitalizations. Simon et al. reported no difference between groups in number of psychiatric hospitalizations at 12 and

24 months.^{231, 232} However, Kessing et al. found that treatment with systematic or collaborative care resulted in a significant decrease in readmissions compared with the inactive comparator. In addition, the cumulative duration of readmissions was shorter the in intervention group.²²⁸ One low risk of bias study reported information on deaths and suicide rates. Bauer et al. (n=330) reported no differences between groups in number of deaths. The study reported that one person who received usual care attempted suicide.²²⁷

Systematic or Collaborative Care Versus Active Control

None of the eligible studies on systematic or collaborative care compared the intervention with an active comparator.

Family or Partner Interventions

We identified nine publications reporting six unique studies on the use of FPI as a treatment for BD.²³⁵⁻²⁴³ [Appendix M](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes. We were unable to draw conclusions for FPI due to insufficient evidence.

Family or Partner Interventions Versus Inactive Control

We identified four publications reporting two unique studies on the effect of FPI compared with an inactive comparator. One study was rated low risk of bias.²³⁵ One study was rated moderate to high risk of bias due to differences reporting randomization and attrition across publications.^{238, 239, 242} Study sample sizes ranged from 58 to 92. Subjects in one study were euthymic while the other study enrolled participants with a current episode (depressive, manic, or mixed). The FPI consisted of either 6 or 12 weekly sessions. Inactive comparator comparator included treatment as usual and pharmacotherapy.

Table 40 summarizes the key characteristics of the studies. [Appendix M](#) provides details.

Table 40. Population and inclusion criteria for studies of FPI versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographic s	Key Exclusion s
D'Souza, 2010 ²³⁵ Singlesite Australia Low ROB 19428117	Patient/companion group psychoeducation consisting of discussion of symptoms, medications, and warning signs, and resources as well as psychotherapy -12 weekly sessions, 90 minutes each session	Treatment as usual: Community based case management involving weekly review with a mental health clinician and a monthly medical review -Weekly sessions for 45 minutes	BD-I or II; MINI Euthymic/Maintenance	Mean Age 41 (19-60) 52% Female Race NR N=58	Substance Abuse; Other Mental Health; Labs/Other Conditions

Author, Year Single- Multisite Local/ Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographic s	Key Exclusion s
Miller 2008 ²³⁸ Solomon 2008 ²⁴² Miller 2004 ²³⁹ Singlesite US Moderate/ High ROB 15555694 19032711 18363424	Individual or group family therapy consisting of semi- structured family interventions. Individual therapy was based on McMaster Model of Family Function and group therapy included sessions focused on signs and symptoms, patient and family perspectives, and coping mechanisms. -6 to 10 sessions of family therapy, 50 minutes per session OR -6 weekly group sessions, 90 minutes per session	Pharmacotherapy: Mood stabilizer with other medications as necessary	BD-I; DSM-III Current bipolar mood episode. Severe episodes not reported	Mean Age 39 (18-65) 57% Female Race NR N=92	Substance Abuse

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; FPI=Family or partner interventions; MINI=Mini-International Neuropsychiatric Interview; N=number; NOS=Not otherwise specified; NR=not reported; ROB-risk of bias

Relapse

Evidence was insufficient for the effect of FPI on relapses when compared with an inactive comparator due to inconsistent findings and imprecision. Two studies enrolling 150 participants reported number of relapses.^{235, 239 242} Evidence regarding the effect of FPI on relapses was mixed. At 15 months, D'Souza et al. reported fewer relapses for those who received FPI.²³⁵ Miller et al. (n=92), reported no difference between groups in the proportion of participants that experienced recovery or time to recovery across 28 months.²³⁹ In a high risk of bias publication, the study also reported that among the subset of 53 patients who recovered from their intake mood episode, there was no difference between those who received FPI (either individual or group) and the inactive comparator group in relapses across the 28 months of the study.²⁴² There was also no difference between groups in time to recurrence.²⁴²

Symptom Scores

Evidence was insufficient for the effect of the FPI on depression and mania outcomes when compared with an inactive comparator due to unclear consistency and imprecision. One low risk of bias study enrolling 58 participants reported symptom scores and provided sufficient data to calculate effect sizes.²³⁵ D'Souza et al. found no difference between groups in depression

symptoms at 15 months.²³⁵ However, a statistically significant difference in mania symptoms was reported at 15 months, with those that received FPI experiencing less symptoms.²³⁵

Additional Outcomes

One publication with high risk of bias reported information on hospitalizations.²⁴² Among the subset of 53 patients who recovered from their intake mood episode, the study found that there was a significant difference between groups in frequency of hospitalizations. While the frequency of hospitalizations was relatively similar between those who received individual family therapy and those who received the inactive comparator, participants who received group family therapy had fewer hospitalizations.²⁴²

Family or Partner Therapy Versus Active Control

We identified five publications reporting four unique studies on the effect of FPI when compared with active comparator. Two studies were rated low risk of bias,^{236, 237, 240} and two were moderate.^{241, 243} Study sample sizes ranged from 53 to 101. The studies did not exclude individuals based on the current clinical state (i.e., including euthymic state or a current depressive, hypomanic, manic, or mixed episode). Three of four studies included psychoeducation as a component of the intervention. In addition, three of the four studies had an intervention span of 9 months. Active comparators included family education with crisis management, treatment as usual with enhanced assessment and monitoring, and individual treatment.

Table 41 summarizes the key characteristics of the studies. [Appendix M](#) provides details.

Table 41. Population and inclusion criteria for studies of FPI versus active comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Wenze, 2015 ²⁴³ Singlesite US Moderate ROB 26117247	Integrated Treatment Adherence Program based on a cognitive behavioral approach focused on transitioning patients from acute to maintenance care using patient and family or significant other meetings in person and via telephone. -3 individual in-person sessions, 60 minutes per session; a 60 minute in-person session with family session, and 11 phone contacts held separately with subject and designated family member or significant other	Enhanced Assessment and Monitoring consisting of treatment as usual with enhanced monitoring (battery of interview-rated and self-report assessments followed by feedback letters)	BD-I, II, or NOS; DSM-IV No current clinical state excluded. Severe episodes not reported	Mean Age 47 (24-68) 50% Female 90% White N=30	Other Mental Health; Pregnant/Nursing; Labs/Other Conditions
Miklowitz, 2003 ²³⁶ Miklowitz, 2000 ²³⁷ Multisite US Low ROB 11018229 12963672	Family-focused therapy with pharmacotherapy consisting of psychoeducation, developing communication skills, and learning a framework for defining problems and implementing solutions. -Up to 21 family or marital sessions over 9 months, 60 minutes per session	Family education (2 sessions) and crisis management consisting of treatment as usual with emergency counseling sessions as needed and monthly telephone calls with patient	BD-I; DSM-III No current clinical state excluded. Severe episodes not reported	Mean Age 36 (18-56) 63% Female Race NR N=101	Substance Abuse; Neurological Disorders; Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Rea, 2003 ²⁴⁰ Multisite US Low ROB 12795572	Family-focused treatment (with medication management) consisting of psychoeducation, communication enhancement training, and problem-solving skills training -21 therapy sessions over 9 months (60 minutes per session) with 1 year of medication management	Individual treatment (with medication management) consisting of meeting a therapist to receive education about illness and symptoms, discuss problem-solving, and establishing goals. -21 therapy sessions over 9 months (30 minutes per session) with 1 year of medication management	BD-I, II, or NOS; DSM-III Manic	Mean Age 26 (18=46) 57% Female 60% White N=53	Substance Abuse; Labs/Other Conditions
Simoneau. 1999 ²⁴¹ US Multisite Moderate ROB 10609423	Family-focused therapy (with medication management) consisting of psychoeducation, communication-enhancement training, and problem-solving skills training -21 sessions over 9 months	Crisis management with naturalistic follow-up (with medication management) consisting of two sessions of home-based family education, crisis intervention as needed, telephone counseling and individual support sessions as needed, and monthly contacts. -9 months of management	BD (Not Specified); DSM-III No current clinical state excluded. Severe episodes not reported	Mean Age 34 (18-57) 54% Female Race NR N=79	Substance Abuse; Labs/Other Conditions

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; N=number; NOS=Not otherwise specified; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of FPI on relapse due to strong imprecision. Two low or moderate risk of bias studies enrolling 154 participants reported information on relapses.^{236, 237, 240} Miklowitz et al. (n=101) had no difference between groups at 12 months; however there were fewer relapses at 24 months in participants who received the family/partner therapy.^{236, 237} In addition, Rea et al. (2003) (n=53) reported no difference between groups in number of relapses at 12 months; however there was a significant difference between groups in the 1-year period post-treatment (24 months total) with fewer relapses reported for the FPI group.²⁴⁰

Symptom Scores

Evidence was insufficient for the effect of FPI on depression and mania symptoms, due to strong imprecision. Three low or moderate risk of bias studies enrolling 210 subjects reported symptom scores. Two studies were rated low risk of bias and two were rated moderate risk of bias.^{236, 237, 241, 243} Only one study provided sufficient evidence to calculate effect sizes. Two studies reported a significant difference in depression symptoms at various time points, all favoring participants that received FPI.^{236, 237, 243} One study reported no difference in mania symptoms at 12 or 24 months.^{236, 237} Wenze et al. (n=30) reported a significant difference between groups at 6 months, with less manic symptoms in the group that received FPI.²⁴³ In addition, Simoneau et al. (1999) (n=79) reported a generalized symptom score finding that participants who received FPI showed a greater improvement in BD symptoms than those who received the active comparator at one year post-treatment.²⁴¹

Function

No measures of global function were reported. Evidence was insufficient for the effect of FPI on health and disability due to unclear consistency and imprecision. For other measures of function, one moderate risk of bias study of enrolling 30 participants reported that individuals who received the FPI had greater improvements in health and disability at 6 months than those who received the active comparator.²⁴³

Additional Outcomes

One moderate risk of bias study reported information on emergency room visits and hospitalizations. Wenze et al. (n=30) reported that no significant difference between groups in either outcome at 6 months.²⁴³

Interpersonal and Social Rhythm Therapy

We identified seven publications reporting two unique studies on IPSRT as a treatment for BD.²⁴⁴⁻²⁵⁰ [Appendix N](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes. We were unable to draw conclusions for IPSRT interventions due to insufficient evidence.

Interpersonal and Social Rhythm Therapy Versus Inactive Control

Five publications reported one high risk of bias study, the Maintenance Therapy in Bipolar Disorder trial, compared IPSRT to intensive clinical management.^{244-247, 250} Total enrollment for the trial was 181 subjects. The trial randomized patients to an initial 12 weeks of either IPSRT or intensive clinical management. All participants received pharmacotherapy. Patients were then randomized again after 12 weeks to 2 years of additional monthly sessions of either IPSRT or

intensive clinical management. Sample sizes across the publications ranged from 32 to 175 participants.

Table 42 describes the intervention and comparator. [Appendix N](#) provides details.

Table 42. Population and inclusion criteria for studies of IPSRT versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Maintenance Therapies in Bipolar Disorder Frank, 1997 ²⁴⁴ Frank, 1999 ²⁴⁷ Rucci, 2002 ²⁵⁰ Frank, 2005 ²⁴⁵ Frank, 2008 ²⁴⁶ US Multisite High ROB 9171907 10609422 12091194 16143731 18829872	IPSRT (acute, maintenance, or both) focused on maintaining regular daily routines, identification and management of potential triggers and interpersonal psychotherapy. -Acute weekly treatment until remission followed by biweekly sessions for 12 weeks and monthly treatment to 24 months, 45 to 55 minutes per session	Clinical management (acute, maintenance, or both) consisting of medical management of BD (education, review of symptoms, management of adverse effects) - Acute weekly treatment until remission followed by biweekly sessions for 12 weeks and monthly treatment to 24 months, 20 to 25 minutes per session	BD-I or schizoaffective disorder, manic type; DSM-IV Depressive, Manic, or Mixed	Mean Age 35 (18-55) 59% Female 94% White N=38-175	Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; IPSRT=Interpersonal and Social Rhythm Therapy; N=number; NOS=Not otherwise specified; NR=not reported

Evidence was insufficient for all reported outcomes (relapse, depression symptoms, mania symptoms, and non-global function) due to high study limitations, unclear consistency, and imprecision. Overall, the assignment of maintenance treatment had no effect on outcomes. Results at 52 weeks showed no difference between groups in risk of recurrence.²⁴⁷ At 2 years, there was no difference between groups in the proportion achieving remission.²⁴⁶ After 2 years of acute and maintenance treatment, no difference was seen between groups in depression or mania symptoms.^{244, 245}

Global functioning was not measured. For non-global measures of function, receiving IPSRT as an acute treatment appeared to improve occupational functioning compared with intensive clinical management. However, the difference was lost after 2 years of maintenance treatment; occupational functioning across groups was nearly identical.²⁴⁶ The study reported reductions in the suicide attempts compared to the period before study initiation; however, groups did not differ in the number of suicide attempts.²⁵⁰

Interpersonal and Social Rhythm Therapy Versus Active Control

Two publications reported one low risk of bias study, which compared IPSRT to specialist supportive care in 100 adolescents and young adults.^{248, 249} The trial randomized participants to either IPSRT or specialist supportive care, the latter consisting of supportive psychotherapy and psychoeducation.

Table 43 describes the intervention and comparator. [Appendix N](#) provides details.

Table 43, Population and inclusion criteria for studies of IPSRT versus active comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Inder, 2016 ²⁴⁹ Inder, 2015 ²⁴⁸ Singlesite New Zealand Low ROB 25346391 26698820	IPSRT consisting of interpersonal psychotherapy with a focus on social routines and achieve of goals. -Weekly sessions for 3 months, fortnightly for up to 6 months, and then fortnightly to monthly from 6 to 18 months (frequency tailored to patient needs)	Specialist supportive care consisting of supportive psychotherapy and psychoeducation -Weekly sessions for 3 months, fortnightly for up to 6 months, and then fortnightly to monthly from 6 to 18 months (frequency tailored to patient needs)	BD-I, II, or NOS; DSM-IV No current clinical state excluded. Severe episodes not reported	Mean Age 27 (15-36) 76% Female Race NR N=100	Substance Abuse

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; IPSRT=Interpersonal and Social Rhythm Therapy; N=number; NOS=Not otherwise specified; NR=not reported; ROB=risk of bias

Evidence was insufficient for all reported outcomes (depression, mania, and nonglobal function) due to unclear consistency and imprecision. The study did not report relapse. At 6 and 18 months, no difference was seen between groups in depression or mania symptoms.²⁴⁸ Global functioning was not measured. However, groups did not differ in social functioning at 6 months.²⁴⁸ At approximately 3 years (following an 18 month intervention and 18 month follow-up), the number of suicide attempts and other self-injury attempts was reduced from baseline. There was no information regarding differences between groups in self-injury attempts.²⁴⁹

Combination Interventions

We identified six publications reporting five unique studies on combinations of psychosocial interventions for BD.²⁵¹⁻²⁵⁶ [Appendix O](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes. We were unable to draw conclusions for combination interventions due to insufficient evidence.

Combination Interventions Versus Inactive Control

Four publications reporting three unique studies examined the effect of combination interventions when compared with an inactive comparator.²⁵¹⁻²⁵⁴ Two studies were rated low risk of bias,²⁵¹⁻²⁵³ one was moderate,²⁵⁴ and one was high.²⁵³ Study sample sizes ranged from 40 to 122. Two studies did not exclude participants based on the current clinical state (i.e., including euthymic or a current manic, hypomanic, mixed or depressive episode). Components of the combination interventions used in the studies varied, with no consistency across the studies. One study used an online format. Intervention length ranged from 20 weeks to 6 months. Inactive comparisons were generally standard psychopharmacological treatment and clinical management without any form of psychotherapy.

Table 44 summarizes the key characteristics of the studies. [Appendix O](#) provides details.

Table 44. Population and inclusion criteria for studies of combination interventions versus inactive comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Gonzalez-Isasi, 2014 ²⁵¹ Gonzalez-Isasi, 2010 ²⁵² Singlesite Spain Low ROB 20444503 23276524	Group psychoeducation and CBT consisting of sessions about their disorder, the relationship between thoughts and feelings, anxiety control techniques, cognitive restructuring, problem-solving and self-esteem, and social skills. -20 weekly sessions, 90 minutes each	Standard pharmacologic treatment (mood stabilizers, antipsychotics, and/or benzodiazepine) adjusted by psychiatrist	BD-I or II; DSM-IV Euthymic or Subsyndromal (i.e., not meeting current bipolar episode full criteria)	Mean Age 41 (18-63) 48% Female Race NR N=40	Labs/Other Conditions
Todd, 2014 ²⁵⁴ Singlesite UK Moderate ROB 25129531	Interactive, online recovery informed self-management intervention (Living with Bipolar) based on both psychoeducation and CBT. Ten interactive modules to help participants learn more about bipolar experiences, increase self-esteem and self-efficacy for managing BD, increase ability to self-manage, and develop interpersonal skills. Modules included case studies and mood checking tools. -Access to program for 6 months	Wait list control receiving treatment as usual (general practitioner and/or specialist mental health services).	BD-I or II; Self-report and MDQ score No current clinical state excluded. Severe episodes not reported	Mean Age 43 (21-65) 72% Female 89% White N=122	None

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Miklowitz 2003 ²⁵³ Multisite US High ROB 12633127	Individual IPSRT and family (or partner) therapy. Individual IPSRT consisted of identifying interpersonal problems, using Social Rhythm Metric form, managing symptoms and identifying triggers, and relapse prevention. Family therapy involved education about BD, identification of triggers, communication enhancement, and problem-solving. -25 sessions of individual therapy and 25 sessions of family-focused therapy (frequency adapted to patient needs)	Treatment as usual: Crisis management (not described, comparison group from previous clinical trial)	BD-I or II; DSM-IV No current clinical state excluded. Severe episodes not reported	Mean Age 36 (18-55) 60% Female 89% White N=100	Substance Abuse; Neurological Disorders

BD=Bipolar Disorder; CBT=Cognitive Behavioral Therapy; DSM= Diagnostic and Statistical Manual of Mental Disorders; IPSRT=Interpersonal and Social Rhythm Therapy; MDQ=Mood Disorder Questionnaire; N=number; NOS=Not otherwise specified; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of combination interventions on relapse when compared with an inactive comparator due to high study limitations, unclear consistency, and imprecision. A high risk of bias cohort study enrolling 100 participants reported number of relapses finding no difference between groups at 12 months. However, individuals who received the combination intervention had a longer time to recurrence than those who received the inactive comparator.²⁵³

Symptom Scores

Evidence was insufficient for the effect of combination interventions on depression and mania symptoms when compared with an inactive comparator, due to moderate study limitations and strong imprecision. Three low to high risk of bias studies (enrolling 262 participants) reported symptom scores.²⁵¹⁻²⁵⁴ All three studies found that individuals receiving combination intervention had less depressive symptoms than those that received an inactive comparator.²⁵²⁻²⁵⁴ Gonzalez-Isasi et al. (n=40) found that this trend continued long-term, finding a significant difference between groups at 5 years.²⁵¹

Two low to high risk of bias studies reported results for mania symptoms. Rated low risk of bias, Gonzalez-Isasi et al. (n=40) reported a significant difference in mania symptoms at the initial outcome time points (11 and 17 months) and 5 years.^{251, 252} Rated high risk of bias, Miklowitz et al. (n=100) found no difference between groups at 12 months.²⁵³

Function

No measures of global function were reported. Evidence was insufficient for other measures of function due to moderate study limitations, unclear consistency, and imprecision. One moderate risk of bias study enrolling 122 participants reported a significant difference between groups in both quality of life and social functioning at 6 months, favoring the combination intervention.²⁵⁴

Additional Outcomes

Rated low risk of bias, Gonzalez-Isasi et al. (n=40) reported data on hospitalizations, finding fewer hospitalizations at 17 months for a combination intervention compared with an inactive comparator. However, there was no difference between groups in hospitalizations at 11 months or 5 years.^{251, 252}

Combination Interventions Versus Active Control

Two studies compared combination interventions with an active comparator.^{255, 256} One study was rated moderate risk of bias,²⁵⁶ the other study was high.²⁵⁵ Sample sizes ranged from 79 to 463. Included populations varied across the studies with two including participants in acute episodes. Components of the interventions and comparators also varied, with no consistency across the two studies.

Table 45 summarizes the key characteristics of the studies. [Appendix O](#) provides details.

Table 45. Population and inclusion criteria for studies of combination interventions versus active comparators

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Fagiolini 2009 ²⁵⁶ Multisite US Moderate ROB 19500091	Enhanced clinical intervention and specialized care for BD. Enhanced clinical intervention consisted of 10 basic elements plus specific modules for young, elderly, and African American patients. Elements consisted of education (on disorder, medications, sleep) and management (review of symptoms, discussion and management of side effects, discussion of early warning signs). Additional non-specific support provided to both patient and families. -Weekly enhanced clinical sessions for 12 weeks, then every other week for 8 weeks, and then monthly for remaining time or until they achieved recurrence	Specialized care for BD consisting of a manualized system of clinical management included assessment of quality of life, standardized assessments of mood, comprehensive medical evaluations, frequent visits with treatment team, pharmacological treatment and tracking and monitoring of visits.	BD-I, II, or NOS or schizoaffective bipolar subtype disorder; DSM-IV for adults, KSADS-PL for adolescents Any Episode	Mean Age 41 (12-75) 61% Female 83% White N=463	Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions
Zaretsky 2008 ²⁵⁵ Multisite Canada High ROB 18674402	Psychoeducation and CBT. CBT was based on Basco and Rush manual and emphasized collaborative goal setting, cognitive restructuring, problem-solving, and enhancing interpersonal communication. -7 weekly, audiotaped individual sessions of psychoeducation and 13 weekly, audiotaped individual sessions of CBT	Psychoeducation based on the first five chapters of the Basco and Rush CBT manual. -7 weekly, audiotaped individual sessions	BD-I or II; NR Euthymic/ Maintenance	Mean Age 40 (18-62) Sex NR Race NR N=293	Substance Abuse; Schizoaffective; Other Mental Health; Neurological Disorders; Labs/Other Conditions

BD=Bipolar Disorder; CBT=Cognitive Behavioral Therapy; DSM= Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL=; N=number; Kiddie Schedule for Affective Disorders and Schizophrenia; NOS=Not otherwise specified; NR=not reported; ROB=risk of bias

Relapse

Evidence was insufficient for the effect of combination interventions on relapse due to high study limitations, unclear consistency, and imprecision. One high risk of bias study enrolling 79 participants reported no difference between groups in number of relapses.²⁵⁵

Symptom Scores

Evidence was insufficient for the effect of combination interventions on depression and mania symptoms due to high study limitations and imprecision. Two studies enrolling 542 participants reported symptom scores.^{255, 256} One moderate risk of bias study reported no difference between groups at 18 months.²⁵⁶ However, a high risk of bias study reported a significant difference between groups in depressive symptoms at 12 months, favoring the combination intervention.²⁵⁵ One moderate risk of bias study, enrolling 463 participants, reported measures of mania.²⁵⁶ The study found no difference between groups at 18 months.²⁵⁶

Function

Evidence was insufficient for the effect of combination interventions on global function and other measures of function due to moderate study limitations, unclear consistency, and imprecision. One moderate risk of bias study enrolling 463 participants reported measures of function.²⁵⁶ Fagiolini et al. (2009) (n=463) reported no differences between groups in global function at 18 months. The study also reported one measure of quality of life, with participants who received the combination intervention reporting better outcomes at 18 months.²⁵⁶

Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study and Other Interventions

Three studies examined either additional psychosocial interventions not previously described (e.g. self-monitoring),^{202, 257} or represented a unique set of analyses based on a large scale, multisite study, the STEP-BD study.²⁵⁸⁻²⁶¹ STEP-BD assessed effects of intensive, individual CBT, IPSRT, and Family-Focused Therapy in comparison with collaborative care. While STEP-BD had three intervention arms, the primary aim of the study was to compare intensive psychotherapy to psychoeducation-based collaborative care. While, the authors did report some response outcomes by individual intervention arm (provided in Appendix P), the primary analysis of relapse/response and other outcomes like function are reported collapsed as only "intensive psychotherapy."

Table 46 describes the characteristics of these studies. [Appendix P](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes.

Table 46. Population and inclusion criteria for studies of other psychosocial interventions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Deckersbach, 2014 ²⁵⁹ Miklowitz, 2006 ²⁵⁸ Miklowitz, 2007 ²⁶⁰ Miklowitz, 2007b ²⁶¹ Multisite US Moderate/High ROB (based on outcomes/timing) 24077657 16816280 17728418 17404119	Intensive psychotherapy consisting of one of the following: 1) individual CBT consisting of psychoeducation, life events scheduling, cognitive restructuring, problem-solving, strategies for early detection, and interventions for comorbidities, 2) IPSRT consisting of selecting a primary problem area and teaching patients about the Social Rhythm Metric and interpersonal problem resolution, or 3) family-focused therapy which encouraged patients and relatives to develop a common understanding, develop a relapse prevention plan, participate in communication enhancement exercises, and identify and solve problems related to illness or the home environment. -30 50-minute sessions over 9 months	Collaborative care consisting of a reviewing a psychoeducational videotape and workbook and developing a treatment contract. Workbook included information about BD, schedule management and mood charting, improving communication skills, and developing a treatment contract. -Three 50-minute individual sessions	BD-I or II; DSM-IV Major Depressive Episode	Mean Age 40 (18-62) 59% Female 91% White N=293	Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions

Author, Year Single-Multisite Local/Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Depp, 2015 ²⁰² Single-site US Low ROB 25479050	Psychoeducation followed by use of a smart phone that delivered interactive elements via a mobile web-based program that delivered questionnaires and responses based on symptoms or early warning signs -4 sessions of psychoeducation followed by smart intervention (2 surveys per day) for 10 weeks	Psychoeducation followed by binder with paper and pencil mood charts. Monitored remotely via cell phone and had to turn in completed charts at the end of study. -4 sessions of psychoeducation followed by mood charts once per day for 10 weeks	BD Type Not Specified; DSM-IV Any Episode (Without Severe Affective Symptoms)	Mean Age 48 (22-74) 59% Female 70% White N=104	Substance Abuse; Other Mental Health
Faurholt-Jepsen, 2015 ²⁵⁷ Single-site Denmark Low ROB 26220802	Smartphone with self-monitoring system that documented mood, sleep length, activity, medication taken, irritability, cognitive problems, alcohol consumption, stress, menstruation, and early warning signs. Patients could see visual representations of data to self-monitor. System included feedback loop with clinic and contact with study nurse. -6 months of self-monitoring	Smartphone without self-monitoring system and nurse contact if needed. -6 months of smart phone access	BD Type Not Specified; ICD-10 and Schedules for Clinical Assessment in Neuropsychiatry Any Episode (HDRS ≤17 and a YMRS ≤17)	Mean Age 29 (18-60) 82% Female Race NR N=78	Other Mental Health; Pregnant/Nursing; Labs/Other Conditions

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; HDRS=Hamilton depression rating scale; N=number; NOS=Not otherwise specified; NR=not reported; ROB=risk of bias; YRMS=Young mania rating scale.

The STEP-BD study (n=293) compared three different types of intensive psychosocial therapy to collaborative care. The study was rated moderate to high risk of bias study due to differences in reporting across outcomes (moderate for relapse, high for function). The study reported outcomes for relapse and function. Compared with the active comparator, a greater proportion of participants who received any type of intensive psychotherapy recovered. Compared with the other three intensive psychotherapy interventions, a greater proportion of those who received family therapy recovered. In addition, those who received family therapy had the shortest time to recovery.²⁶¹ However, these differences between the intensive psychotherapy interventions were not statistically significant.²⁶¹ In a subset of patients who had been assessed for functioning at baseline, those who received the intensive psychosocial intervention showed statistically significant improvements in overall function compared with those who received the active comparator at 9 months.²⁶⁰ Of the therapies for the intensive psychosocial intervention, the family therapy group showed the largest improvement (mean change from baseline) in function.²⁶⁰

Two low risk of bias studies examined the use of mobile devices for self-monitoring and self-management. Strength of evidence was insufficient for all reported outcomes due to strong imprecision. Depp et al. (n=104) randomized individuals to either self-management via mobile device or mood monitoring via paper and pencil, each following four sessions of psychoeducation.²⁰² The study reported no difference between groups in depression and mania symptoms at 6 months. Faurholt-Jepsen et al. (n=78) randomized participants to use a smart phone for daily monitoring (including receiving clinical feedback) or for normal purposes. The study reported no difference between groups in depression, mania, global function, or quality of life at 6 months.²⁵⁷

Somatic Therapy

One study examined a somatic therapy approach. Table 47 describes the characteristics of this study. [Appendix P](#) provides evidence tables, summary risk of bias assessments, assessments of strength of evidence, and reporting for additional outcomes.

Evidence was insufficient from one small, moderate risk of bias study (n=46) that compared repetitive transcranial magnetic stimulation (rTMS) to sham stimulation.²⁶² At 4 weeks, there was no difference between groups in response or remission rates, or depressive symptoms in individuals experiencing a depressive episode.²⁶²

Table 47. Population and inclusion criteria for studies examining a somatic therapy

Author, Year Single- Multisite Local/ Continent Risk of Bias PMID	Intervention	Comparison	Inclusion Criteria: BD Type; Diagnostic Criteria Current Episode	Demographics	Key Exclusions
Fitzgerald, 2016 ²⁶² Singlesite Australia Moderate ROB 27016659	Repetitive transcranial magnetic stimulation -20 rTMS sessions for four weeks	Sham stimulation -20 sham sessions for four weeks	BD I or II; DSM-IV Depressive Episode	Mean Age 46 (33-59) Female 57% Race NR N = 46	Labs/Other Conditions; Neurological Disorder

BD=Bipolar Disorder; DSM= Diagnostic and Statistical Manual of Mental Disorders; N=number; NR=not reported; ROB=risk of bias; rTMS= repetitive transcranial magnetic stimulation

Interpreting the Findings for Psychosocial and Other Nondrug Treatments

We were largely unable to draw conclusions about the effect of psychosocial interventions for BD. In contrast to previous reviews and metaanalyses, we separately examined studies by both intervention category and comparator type (inactive and active).²⁶³ We also considered the variation of interventions within categories and the variation across the clinical states of enrolled subjects. This limited our ability to draw conclusions from the available evidence.

The evidence base had several limitations. Similar to the drug evidence, a substantial number of studies were excluded due to an attrition rate greater than 50 percent. While this limited the evidence, the findings from these studies were of questionable validity.

Lack of transparency was also a significant limitation. Reporting of outcome time points, number of participants in each arm, and loss to follow-up was at times unclear. Studies inconsistently used scales to measure symptoms of depression, mania, or function. Notably, some studies chose to measure global function while others measured quality of life or social function.

We were unable to assess the impact of interventions on specific phases of BD. The majority of psychosocial interventions studies did not exclude individuals based on their current clinical state, thus investigated mixed samples of individuals in acute hypomanic/manic, mixed, depression episodes, or euthymia. Studies investigating the mixed samples did not examine whether the baseline clinical state affected intervention effect. Additionally, in several instances we could not abstract sufficient data to calculate estimates or verify conclusions presented by studies. Multiple studies provided only test statistics for outcomes without additional data (e.g., means at baseline and outcome time points, mean difference at outcome time points).

The available evidence on other nondrug interventions such as acupuncture or light therapy that may be used to treat BD did not meet our inclusion criteria. Several studies were eliminated because they had high rates of attrition, sample sizes below 10 participants per arm, or did not meet timing criteria (e.g., 3 months for treatment of acute depression). High quality studies, with sufficient sample sizes and appropriate followup periods, are needed to determine whether these interventions benefit individuals with BD.

It is possible that psychosocial interventions provide benefits not expressly or consistently measured in the reviewed literature. Many of the psychosocial interventions included common components of disease education, discussion of triggers, and coping mechanisms. If these common components are active ingredients of a therapeutic effect for psychosocial interventions, then the lack of difference seen in head-to-head comparisons of psychosocial interventions are not surprising; for example the low-strength evidence we found for no differences between CBT versus active comparator in reducing bipolar symptoms. Moreover, some of the outcomes assessed in psychosocial treatment literature, such as rates of relapses into manic or depressive episodes, require long followup intervals to adequately measure change in rates of events that for some patients occur only once every 6-12 months. In other words, true treatment effects may be obscured in studies with followup shorter than 12 months. Finally, studies inconsistently reported other relevant outcomes, such as adherence to drug treatment, which can be improved through educational efforts that help patients accept their diagnoses and improve their coping skills.²⁶⁴

Chapter 8. Discussion

Overview

The evidence base for treatments for bipolar disorder (BD) is sparse and scattered. While a large number of studies were identified, they mapped across a considerable number of treatments and comparators, ultimately yielding few for each actual comparison.

We found no high or moderate strength of evidence for any treatment during any phase of bipolar illness (i.e., acute mania, acute depression, or maintenance). For treatment of acute mania, low-strength evidence was found for atypical antipsychotics compared to placebo for improvements in response and possible remission rates, and improvements in manic symptoms and clinical global impressions. (Table 48) There was also low-strength evidence for improved response and remission rates, as well as manic symptom improvement, for lithium versus placebo. However, most manic symptom improvements were of modest clinical significance, with values that were less than the minimally important difference (MID) but still large enough that a reasonable proportion of participants likely received a benefit. For maintenance phase treatment, only lithium achieved low-strength evidence for benefit for the long-term (1-2 years). No treatments with even low-strength evidence showed favorable outcomes for treatment of depression. Across treatment phases, the large majority of drug comparisons, including almost all comparisons using active comparators, had insufficient evidence from which to draw conclusions.

Table 48. Summary of low-strength* evidence findings by intervention class

Category	Intervention	# Studies/ Design (n analyzed) Timing	Findings
Antipsychotics acute mania	Asenapine vs. placebo	3 RCT (n=936) 3 weeks	Response/Remission: No difference YMRS: Favors Asenapine, MD 4.37 (95% CI 1.27, 7.47; MID 6) CGI-BP-S: Favors Asenapine, MD 0.5 (95% CI 0.29, 0.71; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference
	Cariprazine vs. placebo	3 RCT (n=1,047) 3 weeks	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT=5.6 Remission Rate: Favors Cariprazine, OR 1.95 (95% CI 1.45, 2.63); NNT= 7 YMRS: Favors Cariprazine, MD 5.38 (95% CI 1.84, 8.92; MID 6) CGI-BP-S: Favors Cariprazine, MD 0.54 (95% CI 0.35, 0.73; MID 1) Withdrawal (AE, Lack of Efficacy, Overall): No difference
	Olanzapine vs. placebo	5 RCT (n=1199) 3 weeks	Response: Favors Olanzapine, OR 1.99 (95% CI 1.29, 3.08); NNT=6 Remission: Favors Olanzapine, OR 1.75 (95% CI 1.19, 2.58); NNT=7.5 YMRS: Favors Olanzapine, MD 4.9 (95% CI 2.34, 7.45; MID 6) Withdrawal (Lack of Efficacy, Overall): Favors Olanzapine, MD 0.42 (95% CI 0.29, 0.61)

Category	Intervention	# Studies/ Design (n analyzed) Timing	Findings
		3 RCT (n=611) 3 weeks	CGI-BP-S: No difference
	Quetiapine vs. placebo	4 RCT (n=1,007) 3 weeks	Response: Favors Quetiapine, OR 2.07 (95% CI 1.39, 3.09); NNT=6.2 Withdrawal (Lack of Efficacy): Favors Quetiapine, MD 0.38 (95% CI 0.23, 0.63)
		5 RCT (n=699 forest plot, 1439 total) 3 weeks	YMRS: Favors Quetiapine, MD 4.92 (95% CI 0.31, 9.53; MID 6)
		5 RCT (n=806 forest plot, 1439 total) 3 weeks	CGI-BP-S: Favors Quetiapine, MD 0.54 (95% CI 0.35, 0.74; MID 1)
	Risperidone vs. placebo	2 RCT (n=584) 3 weeks	Response, YMRS, and CGI: Favors Risperidone (not pooled)
	Ziprasidone vs. placebo	2 RCT (n=402) 3 weeks	Response, YMRS, and CGI: Favors Ziprasidone (not pooled)
	Olanzapine vs. Divalproex/ Valproate	2 RCTs (n=635) 3 weeks	Response and Remission: No differenceS
		3 RCTs (n=750) 3 weeks	YMRS: No difference
		3 RCTs (n=578) 3 weeks	CGI: No difference
		4 RCTs (n=867) 3 weeks	Withdrawals: No difference
Mood stabilizers treatments for acute mania	Lithium vs. placebo	1 RCT + 1 IPD (n=325) 3 weeks	Remission and Response: Favors Lithium (not pooled)
		3 RCTs (n=325) 3 weeks	YMRS: Favors Lithium, MD 5.81 (95% CI 2.21, 9.4; MID 6) Withdrawal (Overall): No difference
		1 IPD (n=450) 3 weeks	Withdrawal (Lack of Efficacy, AE): No difference
Other drug treatments for mania	Paliperidone vs. placebo	2 RCT (n=763) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): Favors Paliperidone (possible dose response: No difference at 3 and 6 mg, benefit at 12 mg or median dosage of 9 mg) (not pooled) Withdrawal (AE): No difference
	Topiramate vs. placebo	1 IPD (n=876) 3 weeks	YMRS and Withdrawal (Lack of Efficacy): No difference Withdrawals (Overall): Favors Placebo, 37.2% vs. 26.8%, p=0.005 Withdrawals (AE): Favors Placebo, 6.04% vs. 2.84%, p=0.049
	Topiramate vs. lithium	1 IPD (n=453) 3 weeks	YMRS: Favors Lithium, MD 6.14 (95% CI 3.94, 8.34; MID 6)

Category	Intervention	# Studies/ Design (n analyzed) Timing	Findings
		1 IPD (n=453) 3 weeks	Withdrawal (Overall, AE): No difference
		1 IPD (n=453) 3 weeks	Withdrawal (AE): Favors Topiramate, 2.65% vs. 7.49%, p=0.019
	Allopurinol + lithium vs. placebo + lithium	4 RCT (n=355) 4 weeks	YMRS, CGI, Withdrawal (Overall): No difference
Single drug for maintenance	Lithium vs. placebo	6 RCT (n=1579) 1 to 2 years	Time to overall relapse: Favors Lithium
Psychosocial Interventions	CBT vs. Active Comparators**	5 RCTs (n=461) 6 to 12 months	Depression and Mania symptoms: No difference between groups across range of time periods.
	Systematic or Collaborative Care vs. Inactive Comparators†	2 RCTs (n=599) 7 to 12 months	Relapse: No difference between groups across different time periods.

*All findings are low-strength evidence based generally on moderate study limitations and imprecision; details available in results section and appendixes. ** Active comparators are comparators such as a different psychosocial therapy or peer support.

†Inactive comparators are comparators such as usual care, no intervention.

AE=adverse events; CBT=cognitive behavioral therapy; CGI =Clinical global impression; IPD=Individual patient data; MD=mean difference; NS=not significant; OR=odds ratio; RCT=randomized controlled trial; YMRS=Young mania rating scale

Similarly, only a few studies of psychosocial interventions reached low-strength evidence, finding no differences between particular psychosocial treatment approaches versus active comparators (e.g., another psychotherapeutic approach) for a subset of outcomes. Most comparisons had insufficient evidence to address whether the therapy of interest improves outcomes compared to either inactive (usual care) or active (another therapeutic approach) controls. However, the studies' inclusion criteria and limitations (see section below on limitations) preclude definitive conclusions about the effects of psychosocial interventions.

We were unable to draw a conclusion for several Food and Drug Administration (FDA)-approved drugs for BD. One FDA-approved atypical antipsychotic, aripiprazole, had a limited number of studies and high risk of bias contributing to study limitations for mania treatment evidence. We noted that while a random effect model largely showed no difference between groups in response rates, manic symptom improvement, or withdrawal rates, if a fixed effect model is used, symptom improvements were seen, but at just over half the MID. Fixed effect models only allow inferences for the specific participants in the specific studies, not generalization to the larger applicable population. One FDA-approved drug, chlorpromazine, was used as a comparator in only one study and otherwise not examined. A typical (first generation) antipsychotic, chlorpromazine was approved by the FDA in 1957. The lack of chlorpromazine in the included literature reflects the treatment preference for a different typical antipsychotic, haloperidol, because of the sedative and blood pressure effects of chlorpromazine. Lurasidone, olanzapine, and quetiapine have been approved for depression in BD, based on 6 to 8 week studies, but no studies were identified with at least 3 months followup in this review.

Table 49 provides a list of all comparisons in this review for which we were unable to draw conclusions. Notably, the insufficiency of the evidence does not indicate that the examined

approaches do not have therapeutic benefits, but rather that the scientific evidence is insufficient to draw any conclusions about their therapeutic effects.

Table 49. Interventions/comparators with insufficient strength of evidence for all outcomes (unless otherwise noted)

Category	Drug	Comparator
Antipsychotics for mania	Aripiprazole	Placebo
	Aripiprazole	Haloperidol
	Aripiprazole plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Aripiprazole plus Mood Stabilizers	Haloperidol plus Mood Stabilizer
	Asenapine	Olanzapine
	Asenapine plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Olanzapine (for withdrawal for adverse events only)	Placebo
	Olanzapine	Haloperidol or Lithium or Risperidone
	Olanzapine plus Mood Stabilizer	Mood Stabilizer alone (placebo)
	Olanzapine plus Mood Stabilizers	Mood Stabilizer alone (no placebo)
	Quetiapine	Haloperidol or Lithium
	Quetiapine plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Risperidone	Haloperidol or Lithium
	Risperidone plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Ziprasidone plus Mood Stabilizers	Mood Stabilizer alone (placebo)
	Ziprasidone plus Mood Stabilizer	Chlorpromazine plus Mood Stabilizer
Mood Stabilizers for mania	Haloperidol	Placebo
	Carbamazepine	Placebo
	Divalproex/Valproate	Placebo
	Valproate	No Placebo
	Lithium (for CGI only)	Placebo
	Carbamazepine	Lithium or Valproate
	Carbamazepine	Valproate
	Lamotrigine	Lithium
Other Drugs for mania	Lithium	Haloperidol or Divalproex
	Paliperidone (for Remission, Response, CGI Withdrawal (Overall))	Placebo
	Allopurinol plus Lithium (for Response and Remission)	Lithium alone (placebo)
	Allopurinol plus Lithium	Dipyridamole plus Lithium
	Celecoxib	Placebo
	Dipyridamole plus Lithium	Lithium alone (placebo)
	Donepezil plus Lithium	Lithium alone (placebo)
	Endoxifen	Divalproex
	Gabapentin plus Lithium	Lithium alone (placebo)
	Oxcarbazepine	Divalproex
	Paliperidone Extended Release	Olanzapine or Quetiapine
	Paliperidone plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Tamoxifen	Placebo
	Topiramate plus Risperidone	Divalproex plus Risperidone
	Topiramate and Mood Stabilizer	Mood Stabilizer alone (placebo)
Drugs for depression	Memantine plus Valproate	Valproate alone (placebo)
	Lamotrigine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Antidepressives (paroxetine, bupropion, or both)	Placebo
	Sertraline	Lithium
	Venlafaxine	Lithium
	Lithium and OPT	OPT alone
Drugs for maintenance	Long-acting Injectable Aripiprazole	Placebo
	Aripiprazole	Placebo
	Aripiprazole plus Mood Stabilizer	Mood Stabilizer alone (placebo)

Category	Drug	Comparator
	Carbamazepine	Lithium
	Divalproex	Placebo
	Divalproex plus Lithium	Lithium alone (placebo)
	Fluoxetine	Placebo
	Fluoxetine	Lithium
	Gabapentin plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Lamotrigine	Placebo
	Lamotrigine for pregnant women	Discontinue Mood Stabilizers
	Lamotrigine	Lithium
	Lithium	Placebo
	Lithium	Divalproex/Valproate
	Olanzapine	Placebo
	Olanzapine	Divalproex
	Olanzapine	Lithium
	Olanzapine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Oxcarbazepine plus Lithium	Lithium alone (placebo)
	Paliperidone	Placebo
	Paliperidone	Olanzapine
	Perphenazine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Quetiapine	Placebo
	Quetiapine	Lithium
	Quetiapine plus Mood Stabilizers	Mood Stabilizers alone (placebo)
	Quetiapine and Personalize Treatment	Lithium and Personalized Treatment
	Risperidone	Placebo
	Risperidone	Olanzapine
	Risperidone Long Acting Injectable and Treatment as Usual	Placebo and Treatment as Usual
	Valproic Acid plus Aripiprazole	Lithium plus Aripiprazole
	Venlafaxine	Lithium
	Ziprasidone and Mood Stabilizers	Mood Stabilizers alone (placebo)
Psychosocial Interventions	Psychoeducation	Inactive* Comparators
	Psychoeducation	Active** Comparators
	CBT	Inactive Comparators
	CBT (for Relapse, Global Function, Other Measures of Function)	Active Comparators
	Systematic or Collaborative Care (for Depression, Mania, Global Function, Other Measures of Function)	Inactive Comparators
	Family or Partner Interventions	Inactive Comparators
	Family or Partner Interventions	Active Comparators
	IPSRT	Inactive Comparators
	IPSRT	Active Comparators
	Combination Interventions	Inactive Comparators
	Combination Interventions	Active Comparators
	Other Psychosocial Interventions	Inactive Comparators
Somatic	Repetitive transcranial magnetic stimulation	Sham stimulation

*Inactive comparators include usual care or no intervention. **Active comparators include a different psychosocial therapy, peer support, or similar.

CBT=cognitive behavioral therapy; CGI=Clinical Global Impression; IPSRT= Interpersonal and Social Rhythm Therapy; OPT=Optimal Personalized Treatment

Adverse events in drug studies were somewhat consistently reported for extrapyramidal symptoms, and clinically significant weight gain of greater than 7 percent, but otherwise variably

reported. The harms findings from the included placebo-controlled studies were consistent with information currently reported by FDA labels. (Please see [Appendix Q](#) for drug label information on FDA box warnings and serious adverse events.) While most studies reported no differences between groups, we noted participants using antipsychotics, except quetiapine, reported more extrapyramidal symptoms compared to placebo, and those using olanzapine reported more clinically significant weight gain. For mood stabilizers, participants using carbamazepine reported more severe rash and adverse events compared to placebo. In head-to-head studies, we noted a general pattern of participants receiving atypical antipsychotics fewer extrapyramidal symptoms than participants receiving haloperidol. Unfortunately, psychosocial studies generally did not report attempting to collect harms or other unintentional consequences of receiving psychosocial treatments.

Although we had originally anticipated parsing study findings across several populations and subgroups of interest to address Key Question 4, the vast majority drug treatment studies enrolled participants with bipolar I disorder (BD-I). This held even for maintenance trials as many were extensions of trials with participants who had responded to treatment for an acute manic episode. Given the low to insufficient strength of evidence assessments arising from high study limitations and attrition for the main study research questions, any post-hoc analysis for subgroups would be by definition high risk of bias and not sufficient to draw conclusions. We were therefore unable to address how treatments may differ across different BD populations and subgroups. Likewise, we also did not locate any studies specifically testing interventions in BD patients to address drug treatment side effects for Key Question 3.

Applicability

Applicability of the review findings is challenging. The trials for drug treatments used restrictive exclusion criteria. Over three quarters of the studies for mania also excluded participants experiencing a first manic episode. Moreover, given the inclusion criteria, it is not clear if the current findings extend to populations with bipolar II disorder (BD II), current comorbid substance use, pregnant or nursing women with BD I, or older adults (i.e., age 65 and over). Conversely, the psychosocial trials often did not provide detailed information on the participants and the lack of population description limits the ability to infer from the results. Such a mixed population may mask patterns of effect. With the current information, we cannot determine if or to what extent, this contributed to the few findings of nonsignificance between groups.

Factoring in the issue of high attrition, trials with 20 to 50 percent attrition, such as were used in this review, at best provide an estimate of the effect of a treatment for participants who adhere to, tolerate, and, in some minimal sense, benefit from the treatment. However, at extremely high levels of attrition, even this interpretation is of limited value to clinicians.²⁶⁵ If over 50 percent of patients do not finish treatment, and thus were not followed-up to the end of the trial, then the chances of the trial results being applicable to a new patient would be less than half. Applicability drops even further when we recognize the original randomized sample excludes many subpopulations and co-occurring conditions which reduces how much the sample represents people encountered in regular clinical practice. Likewise, the maintenance trials are most applicable to people with BD-I who respond to initial treatment.

Findings in Relation to What Is Already Known

The findings of this review are consistent with other systematic reviews of treatments for BD, although, given the attention this review paid to the role of attrition, more restricted in positive findings. Compared to published Cochrane reviews, our findings were generally consistent, although somewhat more conservative. We also found benefit for olanzapine and risperidone compared to placebo for mania, and benefit for lithium compared to placebo for maintenance.²⁶⁶⁻²⁶⁸ Cochrane reviews have reported benefit for several additional antipsychotics compared to placebo for which we found insufficient evidence (aripiprazole, haloperidol as single drug and added to mood stabilizers, and olanzapine or risperidone plus mood stabilizers).^{266, 269-272} However, authors of these reports consistently noted issues with attrition and medication adherence may have impacted their results. Insufficient evidence for psychosocial interventions was consistent across all reviews.^{263, 273}

Limitations of the Comparative Effectiveness Review

There were several limitations of the review. The search strategy relied on previous published reviews to identify relevant studies published prior to 1994. The original date was chosen to reflect the change to DMS-IV diagnostic criteria for BD and to focus review resources on abstracting relevant studies rather than searches for ground that has been otherwise well-tread. We believe we have identified the relevant literature, but the possibility of missing a publication, particularly on lithium, remains.

Several inclusion criteria may also have created limitations. We only included studies if the populations were exclusively diagnosed with BD, or if the bipolar subpopulation results were reported separately. While still relevant for drug treatments, psychosocial treatments in particular that were specific to depression or mania and combined in analyses participants with bipolar and nonbipolar diagnoses might not have been included in this review.

Excluding all outcomes except for time-to-event outcomes from studies with greater than 50 percent attrition hindered our ability to address outcomes of interest that require longer followup in studies of smaller sample sizes. However, as is noted in the section below on limitations of the evidence base, the missing data problems created by high attrition is a counterweight to this limitation. A recent overview of reviews from the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder found that while lithium or anticonvulsants are suggestive for preventing suicide attempts and deaths, more research is needed to before the effects can be confirmed.⁷

Literature on harms was essentially based on identified RCTs. We required studies to be at least prospective cohort studies with comparator arms and clearly reported for BD populations. This led to a number of observational studies being excluded, including observational studies that looked at broad classes of drugs, or individual drugs across broad populations.

We also chose minimum study followup periods of 3 weeks for acute mania studies, 3 months for depression studies, and 6 months for maintenance studies. Many studies for depression treatment and other somatic treatments, such as ECT or light therapy, were excluded due to too short of study followup. Given the chronic nature of BD, the clinical relevance of studies reporting the effects of treatments with shorter followup periods is questionable. For example, if a treatment response to depression is not sustained, does it matter if the initial response to one treatment was faster than another? Moreover, in order to provide evidence that a treatment reduces bipolar episode relapse rates, a study followup longer than 12 months is likely

needed to capture frequency of episodes that may occur once or twice per year for some individuals with bipolar disorder.

Limitations of the Evidence Base

Even though we excluded studies with greater than 50 percent attrition (unless the outcome was time to relapse), one of the great challenges we confronted in conducting this systematic review was deciding how to interpret trial results in the face of often very high attrition rates. In the case of trials evaluating pharmaceutical treatments for acute mania, it was very common for anywhere from 10 to 70 percent of randomized patients to not complete treatment for even 3 weeks trials. In principle, treatment discontinuation need not lead to trial discontinuation, i.e., dropping out of the study and subsequent missing data. A National Research Council (NRC) report on missing data in randomized control trials stressed the importance of continuing to collect data on patients for whom treatment is discontinued, be it due to lack of efficacy, adverse events, or other reasons.²⁵⁹ Unfortunately, while the majority of reports did not explicitly comment on whether treatment discontinuation implied trial dropout, we were generally left with this impression given the common reliance on last-observation carried forward (LOCF) techniques and usage of terms like ‘discontinued’ and ‘percent completing trial’. This means that many, if not most, trials had dropout rates (with subsequent missing data) ranging from 10 to 70 percent. Moreover, trials did not provide details about when in the trial period participants’ last observations were observed, other than generally after baseline. Given the frequency of measurements in these trials, dropout as early as the first week cannot be ruled out.

It is well known that missing outcome data can pose a serious threat to both the internal and external validity of a trial.^{265, 274} Some of this risk can be mitigated with appropriate analytic techniques. The appropriateness of different analytic methods depends upon the assumptions one makes, and the justifiability of these assumptions in the relevant context, about the missing-ness mechanism (the reason the data are missing and the relationship between observed and unobserved data). Ultimately every approach will require untestable assumptions. However, the aforementioned-panel recommends that some analytic approaches, including LOCF, ought to be avoided as their validity depends upon categorically unreasonable assumptions. The LOCF method, while easy, requires an assumption that the health-status of participants who dropped out of the trial would not have changed had future observations been recorded. When this assumption is inappropriate, use of LOCF methods can bias effect estimates. Moreover, estimates of standard errors will understate the true uncertainty surrounding effect estimates due to the added uncertainty of having to impute data, and this increases as the number of periods the value is carried forward increases. This can potentially inflate the type-I error rate.²⁴

Several authors have proposed guidelines for acceptable levels of attrition in RCTs. One guideline suggested that anything greater than 5 percent was cause for concern, and anything greater than 20 percent represented a serious threat to validity.²⁷⁵ Although somewhat arbitrary, this is not without theoretical and empirical support. One simulation study found that, while there was only limited or even no bias in estimates of odds-ratios with attrition rates as high as 60 percent if the mechanism leading to the missing outcome data was unrelated to the value of the missing data (referred to as missing at random, or MAR), estimates were ‘seriously biased’ with even low levels of loss to follow-up when the mechanism for missing data was related to the value of the data (referred to as missing not at random, or MNAR).²⁷⁶ Missing at random is a hard assumption to make with a BD population.

On the other hand, it has been argued that, taken in isolation, the overall amount of attrition in a trial is a poor measure of the level of threat missing data poses to the validity of a trial's conclusions.²⁷⁷ This is because the risk of bias also depends upon the size of the observed treatment effect, the reasons for attrition, the degree that attrition rates and reasons vary across arms, and many other factors that might be specific to a trial and intervention under study. Ideally trial reports would include a discussion of the results of sensitivity analyses performed to assess how, under a range of reasonable assumptions, observed levels of missing data might have influenced the primary results. However, such robustness-analyses were almost universally not performed. We were thus presented with the difficult task of trying to interpret the results of trials with often large percentages of missing outcome data and little to no information on how much risk this level of missing-ness posed to the validity of the trial's primary outcome estimates, statistical inference, and even qualitative conclusions.

We acknowledge the extreme difficulty inherent in studying and treating patients with BD (see below for future research suggestions). Still, while it is reasonable to question the wisdom of the decision made in many of the trials to discontinue patients from the trial once they stop treatment (due to lack of efficacy or adverse events), this problem is not limited to patients with BD.^{23, 265}

As a form of compromise, we used what we considered to be an extremely lenient set of criteria for evaluating risk-of-bias from attrition. First, we excluded any outcomes for which over 50 percent of the data was missing. In the context of pharmaceutical treatment of acute mania, if a trial had less than 50 percent attrition at 3 weeks but greater than 50 percent attrition after this, the former outcomes were included and the latter outcomes were excluded. Any trial with over 50 percent attrition by the first outcome was excluded entirely, but we present the attrition rates in the appendix. For studies with attrition rates between 40 to 50 percent, we considered the withdrawal rates to be a valid, poolable outcome but treated other outcomes and harms as suffering from a high-risk of bias. We note that this criterion did not apply to time-to-event outcomes in trials where patients were discontinued after the event was observed, e.g., patients discontinued from follow-up after suffering a mood-episode in a maintenance trial studying time-to-mood relapse.

The other major challenge of the evidence base was variability and potential accuracy of the diagnostic assessment methods during recruitment processes. Most studies used the DSM criteria current for the study period, but the methods and likely reliability of the patient ascertainment varied. Often, detailed information on diagnostic assessment and statistics reporting interrater reliability were lacking. Given the debate whether the underlying mechanisms support the bipolar types as qualitatively and categorically different or lay on a continuum of the same psychopathological dimensions, it would be important to include more standard information about lifetime history of bipolar episodes assessment. There is also great difficulty in accurately diagnosing comorbid mental health conditions that were commonly treated as exclusion criteria, which also speaks for the need of standardized diagnostic assessments and reporting of interrater reliability statistics. Additional information and rigor in diagnostic assessment would generate a greater sense of confidence about who the study participants represent.

Other common limitations of health and medical research were also present. Industry funding for drug treatments was the most common source of funding. Publication bias for antipsychotics, antidepressants, and psychosocial interventions for depressive disorders has been documented.²⁷⁸⁻²⁸¹ Harms, particularly for drug trials, were variably and inconsistently reported

in formats difficult to aggregate. Usual care was not well-described. Publications often incompletely reported study design and conduct.

Future Research

Since evidence-based medicine relies on three realms--evidence, clinical experience, and patient experience--insufficient evidence means decisions must be informed by the latter two realms. This is an unsatisfying position for both clinicians and patients. Additional research for pharmacological, psychosocial, and somatic treatment of various phases of bipolar disorders, especially maintenance and depression, is needed to provide stronger scientific evidence for clinical decisions in these instances. Since only low-strength evidence was reached for benefit or no difference between groups for any treatment, drug or psychosocial, essentially all Key Questions would benefit from further research.

Acknowledging the difficulty and unavoidable issue of withdrawal in BD treatment research, there are a few possible actions to take: (1) Examine clinical and demographic characteristics that may differentiate participants who withdraw from participants who complete, and incorporate these findings in caveats about potential conclusions of treatment effects. Increased awareness of the clinical and demographic predictors of withdrawal are likely to lead to new studies that can attempt to better address treatment for these specific subsets of population. (2) In combination with examining predictors of withdrawal, it is imperative to better assess reasons for withdrawal of consent and more systematically report reasons outside of side effects and lack of efficacy. Currently, often the reasons for withdrawal of consent are not provided, or are unsatisfyingly vague. (3) If high attrition rates exist in a study, performing sensitivity analyses to determine how different assumptions about missing data would affect the effect size and corresponding confidence intervals would be important prior to drawing conclusions based on the existing data. For example, if minor adjustments in the assumptions about the missing data (e.g., adjustments in symptom severity of potentially missing data) would eliminate the treatment effects in a particular study, this should lead researchers to be highly skeptical of such findings. (4) Assuming some indications that attrition was random, certain statistical techniques are more adept at modeling missing data and not unduly influencing the results, such as average score/observation method or use of multilevel linear mixed modeling.

Future studies of BD treatments will require innovative ways to increase study completion rates (e.g., use of technology for followup assessments and study reminders; “smart” bottles, mobile apps, and pills for assessing study drug adherence; multiple secondary contacts for participants and all-inclusive contact information from cell phones, email, to social media; flexible scheduling outside of business hours, availability at the last minute notice). For example, more longitudinal data analysis techniques for intermittent follow-up would help, but that in turn generates the need for more effort to create data repositories that allow individual patient-level data pooling of these longitudinal studies. This also requires greater funding for research with longer study followup duration.

Future research also needs to attend to subpopulation analyses. It is clinically useful to know what treatments are more effective for patients with early (prior to age 18) versus later age of BD illness onset, older adult patients versus younger adult patients, patients with BD-I versus BD-II or bipolar disorder not otherwise specified (BD NOS), patients with comorbid substance use disorders versus without this comorbidity, or patients with specific demographic characteristics. The lack of evidence for specific subpopulations of patients with BD is a direct result of prevailing inclusion and exclusion criteria. For example, the majority of BD treatment studies

have focused on individuals with BD-I diagnoses. While this practice is understandable for studies focusing on the mania treatment effect, it is less clear in cases of maintenance or depression treatment.

Future research should also endeavor to enroll people with different initial episodes and maintenance stages to fully understand the spectrum of responses. Attention should be given to addressing all states of the illness throughout the treatment stream. Different clinical states could use more attention. For example, is maintenance after acute mania versus a depression episode the same? Does maintenance after an acute episode differ from patients “off the street”? We need to understand the nature of the interventions within the context of clinical practice (co-treatments).

Psychosocial therapies also need to address whether people with BD can benefit from a generalized groups without manualized treatment, or if the treatments need to be specifically designed for BD. For certain psychosocial therapeutic treatments, particular bipolar states may not be as relevant. But where targets are based on theorized mechanisms that are likely to affect manic or depressive symptoms, the populations should match the mechanisms so the study can directly address the question.

Psychosocial studies were more likely than drug studies to have inclusive inclusion criteria, but still outcome results were often not reported separately by BD subtype. Failure to assess subjects based on the current clinical state (i.e., including individuals who are currently euthymic, in acute mania/hypomania, in a mixed state, or in acute depression) may have washed out any effects that interventions may have had for a subset of the sample (e.g., any improvements in depression symptoms for individuals in acute depression at the baseline).

With the possible exception of treatment of acute depressive episodes, most psychosocial interventions for people with BD are designed to be used in concert with other - generally pharmacologic - treatments, and not stand on their own as complete treatments of the syndrome. So perhaps it is unrealistic to look too closely at "effects on symptoms" of psychosocial and behavioral interventions in isolation. Beyond simply augmenting medication effects, behavioral interventions can enhance adherence to treatment, reduce family friction, and promote hopefulness in patients and their families and friends. Consistent collection and reporting of other relevant outcomes, such as adherence to drug treatment, which can be improved through educational efforts that help patients accept their diagnoses and improve their coping skills²⁵⁸ would be beneficial.

Consistent minimum outcome datasets for BD research (and report inter-rater reliability of measures used in the study) would help, including harms or unintended consequences for psychosocial interventions. Consistent minimum methodological rigor is also required at the journal level.

Conclusions

No high or moderate-strength evidence was found for any intervention to effectively treat any phase of any type of BD compared to placebo or an active comparator. Low-strength evidence showed improved mania symptoms for all FDA-approved antipsychotics, except aripiprazole, when compared to placebo for adults with BD-I. Participants using antipsychotics, except quetiapine, reported experiencing more extrapyramidal symptoms compared to placebo, and those using olanzapine reported experiencing more clinically significant weight gain. Low-strength evidence also showed benefit from lithium in the short-term for acute mania and longer time to relapse in the long-term versus placebo in adults with BD-I. Evidence was insufficient for

most nondrug interventions. Low-strength evidence showed no effect for CBT on bipolar symptoms compared with active comparators, or systematic/collaborative care on relapse compared with inactive comparators. We were unable to address questions on subpopulations or treatments to reduce the metabolic change side effects of first line drug treatments. Future studies of BD treatments will require innovative ways to increase study completion rates.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Kotwicki R, Harvey PD. Systematic study of structured diagnostic procedures in outpatient psychiatric rehabilitation: a three-year, three-cohort study of the stability of psychiatric diagnoses. *Innov Clin Neurosci*. 2013 May-Jun;10(5-6):14-9. PMID: 23882436.
3. Ferrari A, Baxter A, Whiteford H. A systematic review of the global distribution and availability of prevalence data for bipolar disorder. *J Affect Disord*. 2011;134(1-3):1-13.
4. Gum A, King-Kallimanis B, Kohn R. Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. *Am J Geriatr Psychiatry*. 2009;17:769-81.
5. Samame C, Martino DJ, Strejilevich SA. Social cognition in euthymic bipolar disorder: systematic review and meta-analytic approach. *Acta Psychiatr Scand*. 2012;125(4):266-80.
6. Sole B, Martinez-Aran A, Torrent C, et al. Are bipolar II patients cognitively impaired? A systematic review. *Psychol Med*. 2011;41(9):1791-803.
7. Schaffer A, Isometsa ET, Tondo L, et al. Epidemiology, neurobiology and pharmacological interventions related to suicide deaths and suicide attempts in bipolar disorder: Part I of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. *Aust N Z J Psychiatry*. 49(9):785-802. PMID: 26185269.
8. Merikangas K, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007 May;64(5):543-52. PMID: 17485606.
9. Brady KT, Sonne S. The relationship between substance abuse and bipolar disorder. *J Clin Psychiatry*. 1995;56(Suppl 3):19-24. PMID: 7883738
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009 Oct;62(10):1006-12. doi: 10.1016/j.jclinepi.2009.06.005. PMID: 19631508.
11. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0*. The Cochrane Collaboration; 2011.
12. Viswanath B, Jose SP, Squassina A, et al. Cellular models to study bipolar disorder: A systematic review. *J Affect Disord*. 2015 11 Jun;184:36-50. doi: <http://dx.doi.org/10.1016/j.jad.2015.05.037>. PMID: 2015111614.
13. Langan D, Higgins JP, Simmonds M. Comparative performance of heterogeneity variance estimators in meta-analysis: a review of simulation studies. *Res Synth Methods*. 2016 Apr 06doi: 10.1002/jrsm.1198. PMID: 27060925.
14. Sidik K, Jonkman JN. A comparison of heterogeneity variance estimators in combining results of studies. *Stat Med*. 2007 Apr 30;26(9):1964-81. doi: 10.1002/sim.2688. PMID: 16955539.
15. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014 Feb 18;14:25. doi: 10.1186/1471-2288-14-25. PMID: 24548571.
16. Rover C, Knapp G, Friede T. Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis with few studies. *BMC Med Res Methodol*. 2015 Nov 14;15:99. doi: 10.1186/s12874-015-0091-1. PMID: 26573817.
17. Gonnemann A, Framke T, Grosshennig A, et al. No solution yet for combining two independent studies in the presence of heterogeneity. *Stat Med*. 2015 Jul 20;34(16):2476-80. doi: 10.1002/sim.6473. PMID: 26040434.

18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* . 2010;36(3):1-48.
19. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
20. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011 Nov;64(11):1187-97. PMID: 21477993.
21. Berkman ND, Lohr K, Ansari M, et al. Grading the strength of a body of evidence when assessing health care interventions for the effective health care program of the Agency for Healthcare Research and Quality: An update. . Rockville, MD: Agency for Healthcare Research and Quality; 2013. (vol. AHRQ Publication No. 13(14)-EHC 130-EF).
22. Atkins D, Chang S, Gartlehner G, et al. Assessing the applicability of studies when comparing medical interventions Agency for Healthcare Research and Quality. January 2011.
23. Leon AC, Mallinckrodt CH, Chuang-Stein C, et al. Attrition in Randomized Controlled Clinical Trials: Methodological Issues in Psychopharmacology. *Biol Psychiatry*. 2006 6/1;59(11):1001-5. doi: <http://dx.doi.org/10.1016/j.biopsych.2005.10.020>.
24. Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. *N Engl J Med*. 2012;367(14):1355-60. doi: doi:10.1056/NEJMSr1203730. PMID: 23034025.
25. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2010 Apr;122(1-2):27-38. doi: <http://dx.doi.org/10.1016/j.jad.2009.12.028>. PMID: 20096936.
26. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states.[Erratum appears in *Bipolar Disord*. 2010 May;12(3):350]. *Bipolar Disord*. 2009 Nov;11(7):673-86. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00748.x>. PMID: 19839993.
27. Landbloom RL, Mackle M, Wu X, et al. Asenapine: Efficacy and safety of 5 and 10mg bid in a 3-week, randomized, double-blind, placebo-controlled trial in adults with a manic or mixed episode associated with bipolar I disorder. *J Affect Disord*. 2016 Jan 15;190:103-10. doi: <http://dx.doi.org/10.1016/j.jad.2015.06.059>. PMID: 26496015.
28. Calabrese JR, Keck PE, Jr., Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015 Mar;76(3):284-92. doi: <http://dx.doi.org/10.4088/JCP.14m09081>. PMID: 25562205.
29. Durgam S, Starace A, Li D, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015 Feb;17(1):63-75. doi: <http://dx.doi.org/10.1111/bdi.12238>. PMID: 25056368 (pubmed) 2014-30788-001(Psychinfo).
30. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *J Affect Disord*. 2015 Mar 15;174:296-302. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.018>. PMID: 25532076.
31. Katagiri H, Takita Y, Tohen M, et al. Efficacy and safety of olanzapine in the treatment of Japanese patients with bipolar I disorder in a current manic or mixed episode: a randomized, double-blind, placebo- and haloperidol-controlled study. *J Affect Disord*. 2012 Feb;136(3):476-84. doi: <http://dx.doi.org/10.1016/j.jad.2011.10.045>. PMID: 22134043.

32. McIntyre RS. Aripiprazole for the maintenance treatment of bipolar I disorder: A review. *Clin Ther*. 2010;32 Suppl 1:S32-8. doi: <http://dx.doi.org/10.1016/j.clinthera.2010.01.022>. PMID: 20152551.
33. Tohen M, Vieta E, Goodwin GM, et al. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *J Clin Psychiatry*. 2008 Nov;69(11):1776-89. PMID: 19014751.
34. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group.[Erratum appears in *Arch Gen Psychiatry* 2002 Jan;59(1):91]. *Arch Gen Psychiatry*. 2000 Sep;57(9):841-9. PMID: 10986547.
35. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord*. 2010 May;12(3):230-43. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00815.x>. PMID: 20565430.
36. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *J Clin Psychiatry*. 2005 Jan;66(1):111-21. PMID: 15669897.
37. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2005 Oct;15(5):573-85. PMID: 16139175.
38. Cutler AJ, Datto C, Nordenhem A, et al. Extended-release quetiapine as monotherapy for the treatment of adults with acute mania: a randomized, double-blind, 3-week trial. *Clin Ther*. 2011 Nov;33(11):1643-58. doi: <http://dx.doi.org/10.1016/j.clinthera.2011.10.002>. PMID: 22054797.
39. McElroy SL, Martens BE, Winstanley EL, et al. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *J Affect Disord*. 2010 Jul;124(1-2):157-63. doi: <http://dx.doi.org/10.1016/j.jad.2009.11.014>. PMID: 19963274.
40. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania. *Br J Psychiatry*. 2005 2005;187(3):229-34. doi: <http://dx.doi.org/10.1192/bjp.187.3.229>. PMID: 16135859.
41. Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *Eur Neuropsychopharmacol*. 2005 Jan;15(1):75-84. PMID: 15572276.
42. Potkin SG, Keck PE, Jr., Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol*. 2005 Aug;25(4):301-10. PMID: 16012271.
43. Keck PE, Jr., Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry*. 2003 Apr;160(4):741-8. PMID: 12668364.
44. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania.[Erratum appears in *Am J Psychiatry*. 2005 Feb;7(1):102]. *Am J Psychiatry*. 2002 Jun;159(6):1011-7. PMID: 12042191.
45. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *J Clin Psychiatry*. 2002 Dec;63(12):1148-55. PMID: 12523875.
46. Xu L, Lu Y, Yang Y, et al. Olanzapine-valproate combination versus olanzapine or valproate monotherapy in the treatment of bipolar mania: A randomized controlled study in a chinese population group. *Neuropsychiatr Dis Treat*. 2015 25 May;11:1265-71. doi: <http://dx.doi.org/10.2147/NDT.S81146>. PMID: 26060401 (pubmed) 2015078440 (embase).

47. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *Br J Psychiatry*. 2005 Sep;187:235-42. PMID: 16135860.
48. Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *Br J Psychiatry*. 2009 Jan;194(1):40-8. doi: <http://dx.doi.org/10.1192/bjp.bp.108.049965>. PMID: 19118324.
49. Kanba S, Kawasaki H, Ishigooka J, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole for the treatment of acute manic or mixed episodes in Asian patients with bipolar I disorder (the AMAZE study). *World J Biol Psychiatry*. 2014 2014;15(2):113-21. doi: <http://dx.doi.org/10.3109/15622975.2012.669047>. PMID: 22540407.
50. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *J Psychopharmacol*. 2006 Jul;20(4):536-46. PMID: 16401666.
51. Jeong HG, Lee MS, Ko YH, et al. Combination treatment with aripiprazole and valproic acid for acute mania: an 8-week, single-blind, randomized controlled trial. *Clin Neuropharmacol*. 2012 May-Jun;35(3):97-102. doi: <http://dx.doi.org/10.1097/WNF.0b013e3182560401>. PMID: 22592508.
52. Vieta E, T'Joan C, McQuade RD, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *Am J Psychiatry*. 2008 Oct;165(10):1316-25. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.07101560>. PMID: 18381903.
53. Suppes T, Eudicone J, McQuade R, et al. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. *J Affect Disord*. 2008 Apr;107(1-3):145-54. PMID: 17904226.
54. Sachs GS, Gaugin BD, Gutierrez-Esteinou R, et al. Antimanic response to aripiprazole in bipolar I disorder patients is independent of the agitation level at baseline. *J Clin Psychiatry*. 2007 Sep;68(9):1377-83. PMID: 17915976.
55. El Mallakh RS, Vieta E, Rollin L, et al. A comparison of two fixed doses of aripiprazole with placebo in acutely relapsed, hospitalized patients with bipolar disorder I (manic or mixed) in subpopulations (CN138-007). *Eur Neuropsychopharmacol*. 2010 Nov;20(11):776-83. doi: <http://dx.doi.org/10.1016/j.euroneuro.2010.07.003>. PMID: 20728318.
56. Keck PE, Jr., Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *J Clin Psychiatry*. 2006 Apr;67(4):626-37. PMID: 16669728.
57. Keck PE, Jr., Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. *Am J Psychiatry*. 2003 Sep;160(9):1651-8. PMID: 12944341.
58. Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *J Affect Disord*. 2009 Jan;112(1-3):36-49. doi: <http://dx.doi.org/10.1016/j.jad.2008.05.014>. PMID: 18835043.
59. Szegedi A, Calabrese JR, Stet L, et al. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *J Clin Psychopharmacol*. 2012 Feb;32(1):46-55. doi: <http://dx.doi.org/10.1097/JCP.0b013e31823f872f>. PMID: 22198448.
60. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *Int Clin Psychopharmacol*. 1999 Nov;14(6):339-43. PMID: 10565800.
61. Niufan G, Tohen M, Qiuqing A, et al. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *J Affect Disord*. 2008 Jan;105(1-3):101-8. PMID: 17531327.

62. Perlis RH, Baker RW, Zarate CA, Jr., et al. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006 Nov;67(11):1747-53. PMID: 17196055.
63. Revicki DA, Paramore LC, Sommerville KW, et al. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. *J Clin Psychiatry*. 2003 Mar;64(3):288-94. PMID: 12716270.
64. Shafti SS. Olanzapine vs. lithium in management of acute mania. *J Affect Disord*. 2010 May;122(3):273-6. doi: <http://dx.doi.org/10.1016/j.jad.2009.08.013>. PMID: 19740546.
65. Shi L, Namjoshi MA, Zhang F, et al. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *Int Clin Psychopharmacol*. 2002 Sep;17(5):227-37. PMID: 12177585.
66. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry*. 2002 Jan;59(1):62-9. PMID: 11779284.
67. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Arch Gen Psychiatry*. 2003 Dec;60(12):1218-26. PMID: 14662554.
68. Conus P, Berk M, Cotton SM, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *Eur Psychiatry*. 2015 Nov;30(8):975-82. doi: <http://dx.doi.org/10.1016/j.eurpsy.2015.09.009>. PMID: 26485297.
69. Houston JP, Tohen M, Degenhardt EK, et al. Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes: a double-blind, placebo-controlled study.[Erratum appears in *J Clin Psychiatry*. 2011 Aug;72(8):1157], [Erratum appears in *J Clin Psychiatry*. 2010 Jan;71(1):93]. *J Clin Psychiatry*. 2009 Nov;70(11):1540-7. doi: <http://dx.doi.org/10.4088/JCP.08m04895vel>. PMID: 19778495.
70. Tohen M, Bowden CL, Smulevich AB, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. *Br J Psychiatry*. 2008 Feb;192(2):135-43. doi: <http://dx.doi.org/10.1192/bjp.bp.107.041301>. PMID: 18245032.
71. Namjoshi MA, Risser R, Shi L, et al. Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. *J Affect Disord*. 2004;81(3):223-9. PMID: 15337326.
72. Baker RW, Brown E, Akiskal HS, et al. Efficacy of olanzapine combined with valproate or lithium in the treatment of dysphoric mania. *Br J Psychiatry*. 2004 Dec;185:472-8. PMID: 15572737.
73. Moreno RA, Hanna MM, Tavares SM, et al. A double-blind comparison of the effect of the antipsychotics haloperidol and olanzapine on sleep in mania. *Braz J Med Biol Res*. 2007 Mar;40(3):357-66. PMID: 17334533.
74. Tohen M, Sutton VK, Calabrese JR, et al. Maintenance of response following stabilization of mixed index episodes with olanzapine monotherapy in a randomized, double-blind, placebo-controlled study of bipolar I disorder. *J Affect Disord*. 2009 Jul;116(1-2):43-50. doi: <http://dx.doi.org/10.1016/j.jad.2008.11.003>. PMID: 19054570.
75. Vieta E, Calabrese JR, Hennen J, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar I manic patients during treatment with olanzapine: analysis of pooled data. *J Clin Psychiatry*. 2004 Oct;65(10):1420-8. PMID: 15491248.
76. Baker RW, Tohen M, Fawcett J, et al. Acute dysphoric mania: treatment response to olanzapine versus placebo. *J Clin Psychopharmacol*. 2003 Apr;23(2):132-7. PMID: 12640214.

77. Baker RW, Milton DR, Stauffer VL, et al. Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *J Affect Disord.* 2003 Jan;73(1-2):147-53. PMID: 12507747.
78. Baldessarini RJ, Hennen J, Wilson M, et al. Olanzapine versus placebo in acute mania: treatment responses in subgroups. *J Clin Psychopharmacol.* 2003 Aug;23(4):370-6. PMID: 12920413.
79. Chengappa KN, Baker RW, Shao L, et al. Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania. *Bipolar Disord.* 2003 Feb;5(1):1-5. PMID: 12656931.
80. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. *The Am J Psychiatry.* 1999 1999;156(5):702-9. PMID: 10327902.
81. Ketter TA, Houston JP, Adams DH, et al. Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. *J Clin Psychiatry.* 2006 Jan;67(1):95-101. PMID: 16426094.
82. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *Am J Psychiatry.* 2003 Jul;160(7):1263-71. PMID: 12832240.
83. Suppes T, Brown E, Schuh LM, et al. Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data. *J Affect Disord.* 2005 Dec;89(1-3):69-77. PMID: 16253344.
84. Novick D, Reed C, Haro JM, et al. Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *Int Clin Psychopharmacol.* 2010 Sep;25(5):257-63. doi: <http://dx.doi.org/10.1097/YIC.0b013e32833b8fe4>. PMID: 20531011.
85. Sanger TM, Tohen M, Vieta E, et al. Olanzapine in the acute treatment of bipolar I disorder with a history of rapid cycling. *J Affect Disord.* 2003 Jan;73(1-2):155-61. PMID: 12507748.
86. Katagiri H, Takita Y, Tohen M, et al. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. *Curr Med Res Opin.* 2012 May;28(5):701-13. doi: <http://dx.doi.org/10.1185/03007995.2012.666961>. PMID: 22356118.
87. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *Int J Neuropsychopharmacol.* 2009 Jul;12(6):773-82. doi: <http://dx.doi.org/10.1017/S1461145708009735>. PMID: 19079815.
88. Tohen M, Chengappa KN, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry.* 2004 Apr;184:337-45. PMID: 15056579.
89. Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry.* 2006 Apr;67(4):509-16. PMID: 16669715.
90. Li H, Ma C, Wang G, et al. Response and remission rates in Chinese patients with bipolar mania treated for 4 weeks with either quetiapine or lithium: a randomized and double-blind study. *Curr Med Res Opin.* 2008 Jan;24(1):1-10. PMID: 18028587.
91. Yatham LN, Vieta E, Young AH, et al. A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. *Int Clin Psychopharmacol.* 2007 Jul;22(4):212-20. PMID: 17519644.
92. Yatham LN, Paulsson B, Mullen J, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania.[Erratum appears in *J Clin Psychopharmacol.* 2005 Apr;25(2):201], [Erratum appears in *J Clin Psychopharmacol.* 2005 Feb;25(1):103]. *J Clin Psychopharmacol.* 2004 Dec;24(6):599-606. PMID: 15538120.

93. Suppes T, Ketter TA, Gwizdowski IS, et al. First controlled treatment trial of bipolar II hypomania with mixed symptoms: quetiapine versus placebo. *J Affect Disord*. 2013 Aug 15;150(1):37-43. doi: <http://dx.doi.org/10.1016/j.jad.2013.02.031>. PMID: 23521871.
94. Nejtek VA, Avila M, Chen LA, et al. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *J Clin Psychiatry*. 2008 Aug;69(8):1257-66. PMID: 18681757.
95. Vieta E, Suppes T, Ekholm B, et al. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. *J Affect Disord*. 2012 Dec 15;142(1-3):36-44. doi: <http://dx.doi.org/10.1016/j.jad.2012.04.014>. PMID: 23062763.
96. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clin Neuropharmacol*. 1998 May-Jun;21(3):176-80. PMID: 9617509.
97. Yatham LN, Grossman F, Augustyns I, et al. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial.[Erratum appears in *Br J Psychiatry*. 2003 Apr;182:369]. *Br J Psychiatry*. 2003 Feb;182:141-7. PMID: 12562742.
98. Hirschfeld RM, Keck PE, Jr., Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2004 Jun;161(6):1057-65. PMID: 15169694.
99. Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010 Jul 15;68(2):156-62. doi: <http://dx.doi.org/10.1016/j.biopsych.2010.01.015>. PMID: 20227682.
100. Sachs GS, Vanderburg DG, Edman S, et al. Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, part 1: results of a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2012 Nov;73(11):1412-9. doi: <http://dx.doi.org/10.4088/JCP.11m07388>. PMID: 23218157.
101. Vieta E, Ramey T, Keller D, et al. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. *J Psychopharmacol*. 2010 Apr;24(4):547-58. doi: <http://dx.doi.org/10.1177/0269881108099418>. PMID: 19074536.
102. Stahl S, Lombardo I, Loebel A, et al. Efficacy of ziprasidone in dysphoric mania: pooled analysis of two double-blind studies. *J Affect Disord*. 2010 Apr;122(1-2):39-45. doi: <http://dx.doi.org/10.1016/j.jad.2009.06.023>. PMID: 19616304.
103. Kushner SF, Khan A, Lane R, et al. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disord*. 2006 Feb;8(1):15-27. PMID: 16411977.
104. Weisler RH, Hirschfeld R, Cutler AJ, et al. Extended-release carbamazepine capsules as monotherapy in bipolar disorder : pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs*. 2006;20(3):219-31. PMID: 16529527.
105. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology*. 2000 May;150(1):15-23. PMID: 10867972.
106. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry*. 1991 Oct;48(10):915-21. PMID: 1929761.
107. Lerer B, Moore N, Meyendorff E, et al. Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry*. 1987 Mar;48(3):89-93. PMID: 3546274.
108. Weisler RH, Kalali AH, Cutler AJ, et al. Efficacy and safety of once- versus twice-daily carbamazepine extended-release capsules for the treatment of manic symptoms in patients with bipolar I disorder. *Psychiatry*. 2008;5(3):35-48. PMID: 22778707.
109. Weisler RH, Kalali AH, Ketter TA, et al. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry*. 2004 Apr;65(4):478-84. PMID: 15119909.

110. El-Mallakh RS, Salem MR, Chopra AS, et al. Adverse event load in bipolar participants receiving either carbamazepine immediate-release or extended-release capsules: a blinded, randomized study. *Int Clin Psychopharmacol*. 2009 May;24(3):145-9. doi: <http://dx.doi.org/10.1097/YIC.0b013e328329b199>. PMID: 19367153.
111. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *J Clin Psychiatry*. 2006 Oct;67(10):1501-10. PMID: 17107240.
112. Hirschfeld RM, Bowden CL, Vigna NV, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended-release in the acute treatment of mania. *J Clin Psychiatry*. 2010 Apr;71(4):426-32. doi: <http://dx.doi.org/10.4088/JCP.08m04960yel>. PMID: 20361904.
113. McElroy SL, Martens BE, Creech RS, et al. Randomized, double-blind, placebo-controlled study of divalproex extended release loading monotherapy in ambulatory bipolar spectrum disorder patients with moderate-to-severe hypomania or mild mania. *J Clin Psychiatry*. 2010 May;71(5):557-65. doi: <http://dx.doi.org/10.4088/JCP.08m04854yel>. PMID: 20361901.
114. Wang Z, Gao K, Kemp DE, et al. Lamotrigine adjunctive therapy to lithium and divalproex in depressed patients with rapid cycling bipolar disorder and a recent substance use disorder: a 12-week, double-blind, placebo-controlled pilot study. *Psychopharmacol Bull*. 2010;43(4):5-21. PMID: 21240149.
115. Bowden CL, Singh V, Weisler R, et al. Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. *Acta Psychiatr Scand*. 2012 Nov;126(5):342-50. doi: <http://dx.doi.org/10.1111/j.1600-0447.2012.01890.x>. PMID: 22708645.
116. Kemp DE, Gao K, Ganocy SJ, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. *J Clin Psychiatry*. 2009 Jan;70(1):113-21. PMID: 19192457.
117. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *Am J Psychiatry*. 2005 Nov;162(11):2152-61. PMID: 16263857.
118. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group.[Erratum appears in JAMA 1994 Jun 15;271(23):1830]. *JAMA*. 1994 Mar 23-30;271(12):918-24. PMID: 8120960.
119. Oquendo MA, Galfalvy HC, Currier D, et al. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior.[Erratum appears in Am J Psychiatry. 2012 Feb;169(2):223]. *Am J Psychiatry*. 2011 Oct;168(10):1050-6. doi: <http://dx.doi.org/10.1176/appi.ajp.2011.11010163>. PMID: 21768611.
120. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry*. 2005 Jan;62(1):37-45. PMID: 15630071.
121. Ichim L, Berk M, Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Ann Clin Psychiatry*. 2000 Mar;12(1):5-10. PMID: 10798820.
122. Licht RW, Nielsen JN, Gram LF, et al. Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). *Bipolar Disord*. 2010 Aug;12(5):483-93. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00836.x>. PMID: 20712749.

123. Bowden CL, Calabrese JR, Ketter TA, et al. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *Am J Psychiatry*. 2006 Jul;163(7):1199-201. PMID: 16816224.
124. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *J Clin Psychiatry*. 2000 Nov;61(11):841-50. PMID: 11105737.
125. Goldberg JF, Calabrese JR, Saville BR, et al. Mood stabilization and destabilization during acute and continuation phase treatment for bipolar I disorder with lamotrigine or placebo. *J Clin Psychiatry*. 2009 Sep;70(9):1273-80. doi: <http://dx.doi.org/10.4088/JCP.08m04381>. PMID: 19689918.
126. Bowden CL, Mosolov S, Hranov L, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. *Int Clin Psychopharmacol*. 2010 Mar;25(2):60-7. doi: <http://dx.doi.org/10.1097/YIC.0b013e328333ac1b>. PMID: 20101186.
127. Amsterdam JD, Luo L, Shults J. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. *Br J Psychiatry*. 2013 2013;202(4):301-6. doi: <http://dx.doi.org/10.1192/bjp.bp.111.104711>. PMID: 23099447.
128. Ahmad A, Sheikh S, Shah T, et al. Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen. *Clin Transl Sci*. 2016 01 Oct;9(5):252-9. doi: <http://dx.doi.org/10.1111/cts.12407>. PMID: 27346789 PMID/611114504 Embase.
129. Arabzadeh S, Ameli N, Zeinoddini A, et al. Celecoxib adjunctive therapy for acute bipolar mania: A randomized, double-blind, placebo-controlled trial. *Bipolar Disord*. 2015 01 Sep;17(6):606-14. doi: <http://dx.doi.org/10.1111/bdi.12324>. PMID: 26291962 (pubmed) 2015329826 (embase).
130. Jahangard L, Soroush S, Haghighi M, et al. In a double-blind, randomized and placebo-controlled trial, adjuvant allopurinol improved symptoms of mania in in-patients suffering from bipolar disorder. *Eur Neuropsychopharmacol*. Jun. 2014 2, 2014(Pagination)doi: <http://dx.doi.org/10.1016/j.euroneuro.2014.05.013>. PMID: 24953766.
131. Weiser M, Burshtein S, Gershon AA, et al. Allopurinol for mania: A randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. *Bipolar Disord*. 2014 2014;16(4):441-7. doi: <http://dx.doi.org/10.1111/bdi.12202>. PMID: 24712840.
132. Fan A, Berg A, Bresee C, et al. Allopurinol augmentation in the outpatient treatment of bipolar mania: a pilot study. *Bipolar Disord*. 2012 Mar;14(2):206-10. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.01001.x>. PMID: 22420596.
133. Astaneh AN, Rezaei O. Adjunctive treatment with gabapentin in bipolar patients during acute mania. *Int J Psychiatry Med*. 2012;43(3):261-71. PMID: 22978083.
134. Yildiz A, Guleryuz S, Ankerst DP, et al. Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Arch Gen Psychiatry*. 2008 Mar;65(3):255-63. doi: <http://dx.doi.org/10.1001/archgenpsychiatry.2007.43>. PMID: 18316672.
135. Chengappa RKN, Schwarzman LK, Hulihan JF, et al. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2006 Nov;67(11):1698-706. PMID: 17196048.
136. Machado-Vieira R, Soares JC, Lara DR, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. *J Clin Psychiatry*. 2008 Aug;69(8):1237-45. PMID: 18681754.

137. Chen J, Lu Z, Zhang M, et al. A randomized, 4-week double-blind placebo control study on the efficacy of donepezil augmentation of lithium for treatment of acute mania. *Neuropsychiatr Dis Treat*. 2013 17, 2013;9:839-45. PMID: 23807849.
138. Bahk WM, Shin YC, Woo JM, et al. Topiramate and divalproex in combination with risperidone for acute mania: a randomized open-label study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005 Jan;29(1):115-21. doi: 10.1016/j.pnpbp.2004.10.013. PMID: 15610953.
139. Berwaerts J, Melkote R, Nuamah I, et al. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. *J Affect Disord*. 2012 May;138(3):247-58. doi: <http://dx.doi.org/10.1016/j.jad.2012.01.047>. PMID: 22377512.
140. Berwaerts J, Xu H, Nuamah I, et al. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *J Affect Disord*. 2012 Jan;136(1-2):e51-60. doi: <http://dx.doi.org/10.1016/j.jad.2010.06.030>. PMID: 20624657.
141. Berwaerts J, Lane R, Nuamah IF, et al. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *J Affect Disord*. 2011 Mar;129(1-3):252-60. doi: <http://dx.doi.org/10.1016/j.jad.2010.09.011>. PMID: 20947174.
142. Vik A, Ravindran A, Shiah IS, et al. A double-blind, placebo-controlled study of adjunctive calcitonin nasal spray in acute refractory mania. *Bipolar Disord*. 2013 2013;15(4):359-64. PMID: 23551803.
143. Grunze H, Kotlik E, Costa R, et al. Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. *J Affect Disord*. 2015 Mar 15;174:70-82. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.013>. PMID: 25484179.
144. Amsterdam JD, Garcia-Espana F, Fawcett J, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol*. 1998 Dec;18(6):435-40. PMID: 9864074.
145. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. *J Clin Psychopharmacol*. 2008 Apr;28(2):171-81. doi: 10.1097/JCP.0b013e318166c4e6. PMID: 18344727.
146. Nierenberg AA, Sylvia LG, Leon AC, et al. Lithium treatment -- moderate dose use study (LiTMUS) for bipolar disorder: rationale and design. *Clinical Trials*. 2009 Dec;6(6):637-48. doi: <http://dx.doi.org/10.1177/1740774509347399>. PMID: 19933719.
147. Kemp DE, Gao K, Fein EB, et al. Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. *Bipolar Disord*. 2012 Nov;14(7):780-9. doi: <http://dx.doi.org/10.1111/bdi.12013>. PMID: 23107222.
148. Lee SY, Chen SL, Chang YH, et al. Genotype variant associated with add-on memantine in bipolar II disorder.[Erratum appears in *Int J Neuropsychopharmacol*. 2014 Jun;17(6):979 Note: Lu, Ru-Band [removed]; Hong, Jau-Shyong [added]]. *Int J Neuropsychopharmacol*. 2014 Feb;17(2):189-97. doi: <http://dx.doi.org/10.1017/S1461145713000825>. PMID: 24103632.
149. Lee S-Y, Chen S-L, Chang Y-H, et al. Add-on memantine to valproate treatment increased HDL-C in bipolar II disorder. *J Psychiatr Res*. 2013 2013;47(10):1343-8. doi: <http://dx.doi.org/10.1016/j.jpsychires.2013.06.017>. PMID: 23870798.
150. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *The N Engl J Med*. 2007 2007;356(17):1711-22. doi: <http://dx.doi.org/10.1056/NEJMoa064135>. PMID: 17392295.

151. Altshuler LL, Sugar CA, McElroy SL, et al. Switch rates during acute treatment for Bipolar II depression with Lithium, Sertraline, or the two combined: A randomized double-blind comparison. *Am J Psychiatry*. 2017 March;174(3):266-76. doi: <http://dx.doi.org/10.1176/appi.ajp.2016.15040558>. PMID: 28135846 PMID/614689619 Embase.
152. Amsterdam JD, Lorenzo-Luaces L, Soeller I, et al. Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: Effectiveness and mood conversion rate. *Br J Psychiatry*. 2016 April;208(4):359-65. doi: <http://dx.doi.org/10.1192/bjp.bp.115.169375>. PMID: 26892848 PMID/609914520 Embase.
153. Lorenzo-Luaces L, Amsterdam JD, Soeller I, et al. Rapid versus non-rapid cycling bipolar II depression: Response to venlafaxine and lithium and hypomanic risk. *Acta Psychiatr Scand*. 2016 01 Jun;133(6):459-69. doi: <http://dx.doi.org/10.1111/acps.12557>. PMID: 26803764 PMID/608565179 Embase.
154. Amsterdam JD, Wang CH, Shwarz M, et al. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: a randomized, parallel group, open-label trial. *J Affect Disord*. 2009 Jan;112(1-3):219-30. doi: <http://dx.doi.org/10.1016/j.jad.2008.03.029>. PMID: 18486235.
155. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *J Clin Psychiatry*. 2010 Apr;71(4):372-80. doi: <http://dx.doi.org/10.4088/JCP.08m04909gre>. PMID: 20409444.
156. Nierenberg AA, Friedman ES, Bowden CL, et al. Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. *Am J Psychiatry*. 2013 Jan 1;170(1):102-10. doi: <http://dx.doi.org/10.1176/appi.ajp.2012.12060751>. PMID: 23288387.
157. Nierenberg AA, McElroy S, Ketter TA, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): A pragmatic six month trial of lithium vs. quetiapine for bipolar disorder. *Bipolar Disord*. 2015 June;17:25-6. doi: <http://dx.doi.org/10.1111/bdi.12306>. PMID: 25306155.
158. Nierenberg AA, Sylvia LG, Leon AC, et al. Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. *Clinical Trials*. 2014 Feb;11(1):114-27. doi: <http://dx.doi.org/10.1177/1740774513512184>. PMID: 24346608.
159. Bowden CL, Karayaal ON, Schwartz JH, et al. Characterizing relapse prevention in bipolar disorder with adjunctive ziprasidone: clinical and methodological implications. *J Affect Disord*. 2013 Jan 10;144(1-2):171-5. doi: <http://dx.doi.org/10.1016/j.jad.2012.04.024>. PMID: 22999893.
160. Balance investigators, Geddes JR, Goodwin GM, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010 Jan 30;375(9712):385-95. doi: [http://dx.doi.org/10.1016/S0140-6736\(09\)61828-6](http://dx.doi.org/10.1016/S0140-6736(09)61828-6). PMID: 20092882.
161. Amsterdam JD, Lorenzo-Luaces L, Soeller I, et al. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. *J Affect Disord*. 2015 06 Jul;185:31-7. doi: <http://dx.doi.org/10.1016/j.jad.2015.05.070>. PMID: 26143402 (pubmed) 2015175772 (embase).
162. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. *Am J Psychiatry*. 2010 Jul;167(7):792-800. doi: <http://dx.doi.org/10.1176/appi.ajp.2009.09020284>. PMID: 20360317.

163. Bobo WV, Epstein RA, Lynch A, et al. A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. *Clin Neuropsychopharmacol*. 2011 Nov-Dec;34(6):224-33. doi: <http://dx.doi.org/10.1097/WNF.0b013e318237709a>. PMID: 22104634.
164. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Arch Gen Psychiatry*. 2000 May;57(5):481-9. PMID: 10807488.
165. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.[Erratum appears in *Arch Gen Psychiatry*. 2004 Jul;61(7):680]. *Arch Gen Psychiatry*. 2003 Apr;60(4):392-400. PMID: 12695317.
166. Bowden CL, Vieta E, Ice KS, et al. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry*. 2010 Feb;71(2):130-7. doi: <http://dx.doi.org/10.4088/JCP.09m05482yel>. PMID: 20122373.
167. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry*. 2003 Sep;64(9):1013-24. PMID: 14628976.
168. Greil W, Kleindienst N. Lithium versus carbamazepine in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified. *Int Clin Psychopharmacol*. 1999 Sep;14(5):283-5. PMID: 10529071.
169. Greil W, Kleindienst N. The comparative prophylactic efficacy of lithium and carbamazepine in patients with bipolar I disorder. *Int Clin Psychopharmacol*. 1999 Sep;14(5):277-81. PMID: 10529070.
170. Greil W, Kleindienst N, Erazo N, et al. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *J Clin Psychopharmacol*. 1998 Dec;18(6):455-60. PMID: 9864077.
171. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders--a randomised study. *J Affect Disord*. 1997 Apr;43(2):151-61. PMID: 9165384.
172. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology*. 2003 Jul;28(7):1374-82. PMID: 12784116.
173. Hartong EG, Moleman P, Hoogduin CA, et al. Prophylactic efficacy of lithium versus carbamazepine in treatment-naive bipolar patients. *J Clin Psychiatry*. 2003 Feb;64(2):144-51. PMID: 12633122.
174. Macfadden W, Alphas L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disord*. 2009 Dec;11(8):827-39. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00761.x>. PMID: 19922552.
175. Marcus R, Khan A, Rollin L, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord*. 2011 Mar;13(2):133-44. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00898.x>. PMID: 21443567.
176. Newport DJ, Stowe ZN, Viguera AC, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disord*. 2008 May;10(3):432-6. doi: <http://dx.doi.org/10.1111/j.1399-5618.2007.00565.x>. PMID: 18402631.
177. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *J Clin Psychiatry*. 2016 Jan;77(1):90-9. doi: <http://dx.doi.org/10.4088/JCP.14m09349>. PMID: 26845264.

178. Prien RF, Point P, Caffey EM, et al. Prophylactic efficacy of lithium carbonate in manic-depressive illness: Report of the veterans administration and national institute of mental health collaborative study group. *Arch Gen Psychiatry*. 1973;28(3):337-41. doi: 10.1001/archpsyc.1973.01750330035006. PMID: 4569674.
179. Suppes T, Vieta E, Liu S, et al. Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). *Am J Psychiatry*. 2009 Apr;166(4):476-88. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.08020189>. PMID: 19289454.
180. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *Am J Psychiatry*. 2006 Feb;163(2):247-56. PMID: 16449478.
181. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *Am J Psychiatry*. 2005 Jul;162(7):1281-90. PMID: 15994710.
182. Vieta E, Cruz N, Garcia-Campayo J, et al. A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. *Int J Neuropsychopharmacol*. 2008 Jun;11(4):445-52. doi: <http://dx.doi.org/10.1017/S1461145708008596>. PMID: 18346292.
183. Vieta E, Manuel Goikolea J, Martinez-Aran A, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *J Clin Psychiatry*. 2006 Mar;67(3):473-7. PMID: 16649836.
184. Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012 Nov;22(11):825-35. doi: <http://dx.doi.org/10.1016/j.euroneuro.2012.03.004>. PMID: 22503488.
185. Vieta E, Owen R, Baudelet C, et al. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. *Curr Med Res Opin*. 2010 Jun;26(6):1485-96. doi: <http://dx.doi.org/10.1185/03007991003779380>. PMID: 20429835.
186. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *J Affect Disord*. 2008 Aug;109(3):251-63. doi: <http://dx.doi.org/10.1016/j.jad.2008.06.001>. PMID: 18579216.
187. Weisler RH, Nolen WA, Neijber A, et al. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *J Clin Psychiatry*. 2011 Nov;72(11):1452-64. doi: <http://dx.doi.org/10.4088/JCP.11m06878>. PMID: 22054050.
188. Woo YS, Bahk WM, Chung MY, et al. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. *Hum Psychopharmacol*. 2011 Dec;26(8):543-53. doi: <http://dx.doi.org/10.1002/hup.1240>. PMID: 22134973.
189. Zarate CA, Jr., Tohen M. Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. *Am J Psychiatry*. 2004 Jan;161(1):169-71. PMID: 14702269.
190. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology*. 2000;42 Suppl 1:2-10. PMID: 11093063.
191. Calabrese JR, Sanchez R, Jin N, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: A double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry*. 2017 March;78(3):324-31. doi: <http://dx.doi.org/10.4088/JCP.16m11201>. PMID: 28146613 PMID/615221995 Embase.

192. Carlson BX, Ketter TA, Sun W, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). *Bipolar Disord.* 2012 Feb;14(1):41-53. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00974.x>. PMID: 22329471.
193. Masand PS, Eudicone J, Pikalov A, et al. Criteria for defining symptomatic and sustained remission in bipolar I disorder: a post-hoc analysis of a 26-week aripiprazole study (study CN138-010). *Psychopharmacol Bull.* 2008;41(2):12-23. PMID: 18668014.
194. Keck PE, Jr., Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry.* 2007 Oct;68(10):1480-91. PMID: 17960961.
195. El-Mallakh RS, Marcus R, Baudelet C, et al. A 40-week double-blind aripiprazole versus lithium follow-up of a 12-week acute phase study (total 52 weeks) in bipolar I disorder. *J Affect Disord.* 2012 Feb;136(3):258-66. doi: <http://dx.doi.org/10.1016/j.jad.2011.11.043>. PMID: 22209190.
196. Solomon DA, Ristow WR, Keller MB, et al. Serum lithium levels and psychosocial function in patients with bipolar I disorder. *Am J Psychiatry.* 1996 Oct;153(10):1301-7. PMID: 8831438.
197. Barnes CW, Hadzi-Pavlovic D, Wilhelm K, et al. A web-based preventive intervention program for bipolar disorder: outcome of a 12-months randomized controlled trial. *J Affect Disord.* 2015 Mar 15;174:485-92. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.038>. PMID: 25554993.
198. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry.* 2003 Apr;60(4):402-7. PMID: 12695318.
199. Colom F, Vieta E, Reinares M, et al. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. *J Clin Psychiatry.* 2003 Sep;64(9):1101-5. PMID: 14628987.
200. Colom F, Vieta E, Sanchez-Moreno J, et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial.[Erratum appears in Br J Psychiatry. 2009 Jun;194(6):571]. *Br J Psychiatry.* 2009 Mar;194(3):260-5. doi: <http://dx.doi.org/10.1192/bjp.bp.107.040485>. PMID: 19252157.
201. de Barros Pellegrinelli K, de OCLF, Silval KI, et al. Efficacy of psychoeducation on symptomatic and functional recovery in bipolar disorder. *Acta Psychiatr Scand.* 2013 Feb;127(2):153-8. doi: <http://dx.doi.org/10.1111/acps.12007>. PMID: 22943487.
202. Depp CA, Ceglowski J, Wang VC, et al. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. *J Affect Disord.* 2015 Mar 15;174:23-30. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.053>. PMID: 25479050.
203. Javadpour A, Hedayati A, Dehbozorgi GR, et al. The impact of a simple individual psycho-education program on quality of life, rate of relapse and medication adherence in bipolar disorder patients. *Asian J Psychiatr.* 2013 Jun;6(3):208-13. doi: <http://dx.doi.org/10.1016/j.ajp.2012.12.005>. PMID: 23642977.
204. Perry A, Tarrier N, Morriss R, et al. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *BMJ.* 1999 Jan 16;318(7177):149-53. PMID: 9888904.
205. Sajatovic M, Davies MA, Ganocy SJ, et al. A comparison of the life goals program and treatment as usual for individuals with bipolar disorder. *Psychiatr Serv.* 2009 Sep;60(9):1182-9. doi: <http://dx.doi.org/10.1176/appi.ps.60.9.1182>. PMID: 19723732.
206. Smith DJ, Griffiths E, Poole R, et al. Beating Bipolar: exploratory trial of a novel Internet-based psychoeducational treatment for bipolar disorder. *Bipolar Disord.* 2011 Aug-Sep;13(5-6):571-7. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00949.x>. PMID: 22017225.

207. Weiss RD, Griffin ML, Greenfield SF, et al. Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. *J Clin Psychiatry*. 2000 May;61(5):361-7. PMID: 10847311.
208. Gumus F, Buzlu S, Cakir S. Effectiveness of individual psychoeducation on recurrence in bipolar disorder; a controlled study. *Archives of psychiatric nursing*. 2015 01 Jun;29(3):174-9. doi: <http://dx.doi.org/10.1016/j.apnu.2015.01.005>. PMID: 26001717.
209. Bilderbeck AC, Atkinson LZ, McMahon HC, et al. Psychoeducation and online mood tracking for patients with bipolar disorder: A randomised controlled trial. *J Affect Disord*. 2016 15 Nov;205:245-51. doi: <http://dx.doi.org/10.1016/j.jad.2016.06.064>. PMID: 27454410 PMID/612460558 Embase.
210. Kallestad H, Wullum E, Scott J, et al. The long-term outcomes of an effectiveness trial of group versus individual psychoeducation for bipolar disorders. *J Affect Disord*. 2016;202:32-8. doi: <http://dx.doi.org/10.1016/j.jad.2016.05.043>. PMID: 27253214 PMID/611342382 Embase.
211. Camacho EM, Ntais D, Jones S, et al. Cost-effectiveness of structured group psychoeducation versus unstructured group support for bipolar disorder: Results from a multi-centre pragmatic randomised controlled trial. *J Affect Disord*. 2017 15 Mar;211:27-36. doi: <http://dx.doi.org/10.1016/j.jad.2017.01.005>. PMID: 614007566.
212. Morriss R, Lobban F, Riste L, et al. Clinical effectiveness and acceptability of structured group psychoeducation versus optimised unstructured peer support for patients with remitted bipolar disorder (PARADES): a pragmatic, multicentre, observer-blind, randomised controlled superiority trial. *The Lancet Psychiatry*. 2016 01 Nov;3(11):1029-38. doi: <http://dx.doi.org/10.1016/S2215-0366%2816%2930302-9>. PMID: 27688021.
213. Weiss RD, Griffin ML, Kolodziej ME, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *Am J Psychiatry*. 2007 Jan;164(1):100-7. PMID: 17202550.
214. Weiss RD, Griffin ML, Jaffee WB, et al. A "community-friendly" version of integrated group therapy for patients with bipolar disorder and substance dependence: a randomized controlled trial. *Drug Alcohol Depend*. 2009 Oct 1;104(3):212-9. doi: <http://dx.doi.org/10.1016/j.drugalcdep.2009.04.018>. PMID: 19573999.
215. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry*. 2006 Apr;188:313-20. PMID: 16582056.
216. Parikh SV, Zaretsky A, Beaulieu S, et al. A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: a Canadian Network for Mood and Anxiety treatments (CANMAT) study [CME]. *J Clin Psychiatry*. 2012 Jun;73(6):803-10. doi: <http://dx.doi.org/10.4088/JCP.11m07343>. PMID: 22795205.
217. Meyer TD, Hautzinger M. Cognitive behaviour therapy and supportive therapy for bipolar disorders: relapse rates for treatment period and 2-year follow-up. *Psychol Med*. 2012 Jul;42(7):1429-39. doi: <http://dx.doi.org/10.1017/S0033291711002522>. PMID: 22099722.
218. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. *Arch Gen Psychiatry*. 2003 Feb;60(2):145-52. PMID: 12578431.
219. Lam DH, Hayward P, Watkins ER, et al. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. *Am J Psychiatry*. 2005 Feb;162(2):324-9. PMID: 15677598.
220. Jones SH, Smith G, Mulligan LD, et al. Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial.[Erratum appears in *Br J Psychiatry*. 2015 Feb;206(2):169]. *Br J Psychiatry*. 2015 Jan;206(1):58-66. doi: <http://dx.doi.org/10.1192/bjp.bp.113.141259>. PMID: 25213157.

221. Harvey AG, Soehner AM, Kaplan KA, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *J Consult Clin Psychol*. 2015 Jun;83(3):564-77. doi: 10.1037/a0038655. PMID: 25622197.
222. Gomes BC, Abreu LN, Brietzke E, et al. A randomized controlled trial of cognitive behavioral group therapy for bipolar disorder. *Psychother Psychosom*. 2011;80(3):144-50. doi: <http://dx.doi.org/10.1159/000320738>. PMID: 21372622.
223. Fava GA, Rafanelli C, Tomba E, et al. The sequential combination of cognitive behavioral treatment and well-being therapy in cyclothymic disorder. *Psychother Psychosom*. 2011;80(3):136-43. doi: <http://dx.doi.org/10.1159/000321575>. PMID: 21372621.
224. Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. *Br J Psychiatry*. 2010 May;196(5):383-8. doi: <http://dx.doi.org/10.1192/bjp.bp.108.058263>. PMID: 20435965.
225. Ball JR, Mitchell PB, Corry JC, et al. A randomized controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. *J Clin Psychiatry*. 2006 Feb;67(2):277-86. PMID: 16566624.
226. Perich T, Manicavasagar V, Mitchell PB, et al. A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. *Acta Psychiatr Scand*. 2013 May;127(5):333-43. doi: <http://dx.doi.org/10.1111/acps.12033>. PMID: 23216045.
227. Bauer MS, McBride L, Williford WO, et al. Collaborative care for bipolar disorder: Part II. Impact on clinical outcome, function, and costs. *Psychiatr Serv*. 2006 Jul;57(7):937-45. PMID: 16816277.
228. Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *Br J Psychiatry*. 2013 Mar;202(3):212-9. doi: <http://dx.doi.org/10.1192/bjp.bp.112.113548>. PMID: 23349295.
229. Kilbourne AM, Goodrich DE, Lai Z, et al. Life Goals Collaborative Care for patients with bipolar disorder and cardiovascular disease risk. *Psychiatr Serv*. 2012 Dec;63(12):1234-8. doi: <http://dx.doi.org/10.1176/appi.ps.201100528>. PMID: 23203358.
230. Kilbourne AM, Post EP, Nosssek A, et al. Improving medical and psychiatric outcomes among individuals with bipolar disorder: a randomized controlled trial. *Psychiatr Serv*. 2008 Jul;59(7):760-8. doi: <http://dx.doi.org/10.1176/appi.ps.59.7.760>. PMID: 18586993.
231. Simon GE, Ludman EJ, Bauer MS, et al. Long-term effectiveness and cost of a systematic care program for bipolar disorder. *Arch Gen Psychiatry*. 2006 May;63(5):500-8. PMID: 16651507.
232. Simon GE, Ludman EJ, Unutzer J, et al. Randomized trial of a population-based care program for people with bipolar disorder. *Psychol Med*. 2005 Jan;35(1):13-24. PMID: 15842025.
233. van der Voort TY, van Meijel B, Goossens PJ, et al. Collaborative care for patients with bipolar disorder: randomised controlled trial. *Br J Psychiatry*. 2015 Mar 19doi: 10.1192/bjp.bp.114.152520. PMID: 25792695.
234. van der Voort TY, van Meijel B, Hoogendoorn AW, et al. Collaborative care for patients with bipolar disorder: Effects on functioning and quality of life. *J Affect Disord*. 2015 Mar 11;179(1):14-22. doi: 10.1016/j.jad.2015.03.005. PMID: 25841077.
235. D'Souza R, Piskulic D, Sundram S. A brief dyadic group based psychoeducation program improves relapse rates in recently remitted bipolar disorder: a pilot randomised controlled trial. *J Affect Disord*. 2010 Jan;120(1-3):272-6. doi: <http://dx.doi.org/10.1016/j.jad.2009.03.018>. PMID: 19428117.
236. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Arch Gen Psychiatry*. 2003 Sep;60(9):904-12. PMID: 12963672.

237. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biol Psychiatry*. 2000 Sep 15;48(6):582-92. PMID: 11018229.
238. Miller IW, Keitner GI, Ryan CE, et al. Family treatment for bipolar disorder: family impairment by treatment interactions. *J Clin Psychiatry*. 2008 May;69(5):732-40. PMID: 18363424.
239. Miller IW, Solomon DA, Ryan CE, et al. Does adjunctive family therapy enhance recovery from bipolar I mood episodes? *J Affect Disord*. 2004 Nov 1;82(3):431-6. PMID: 15555694.
240. Rea MM, Tompson MC, Miklowitz DJ, et al. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. *J Consult Clin Psychol*. 2003 Jun;71(3):482-92. PMID: 12795572.
241. Simoneau TL, Miklowitz DJ, Richards JA, et al. Bipolar disorder and family communication: effects of a psychoeducational treatment program. *J Abnorm Psychol*. 1999 Nov;108(4):588-97. PMID: 10609423.
242. Solomon DA, Keitner GI, Ryan CE, et al. Preventing recurrence of bipolar I mood episodes and hospitalizations: family psychotherapy plus pharmacotherapy versus pharmacotherapy alone. *Bipolar Disord*. 2008 Nov;10(7):798-805. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00624.x>. PMID: 19032711.
243. Wenzel SJ, Gaudiano BA, Weinstock LM, et al. Adjunctive psychosocial intervention following Hospital discharge for Patients with bipolar disorder and comorbid substance use: A pilot randomized controlled trial. *Psychiatry Res*. 2015 Aug 30;228(3):516-25. doi: 10.1016/j.psychres.2015.06.005. PMID: 26117247.
244. Frank E, Hlastala S, Ritenour A, et al. Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. *Biol Psychiatry*. 1997 Jun 15;41(12):1165-73. PMID: 9171907.
245. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry*. 2005 Sep;62(9):996-1004. PMID: 16143731.
246. Frank E, Soreca I, Swartz HA, et al. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. *Am J Psychiatry*. 2008 Dec;165(12):1559-65. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.07121953>. PMID: 18829872.
247. Frank E, Swartz HA, Mallinger AG, et al. Adjunctive psychotherapy for bipolar disorder: effects of changing treatment modality. *J Abnorm Psychol*. 1999 Nov;108(4):579-87. PMID: 10609422.
248. Inder ML, Crowe MT, Luty SE, et al. Randomized, controlled trial of Interpersonal and Social Rhythm Therapy for young people with bipolar disorder. *Bipolar Disord*. 2015 Mar;17(2):128-38. doi: 10.1111/bdi.12273. PMID: 25346391.
249. Inder ML, Crowe MT, Luty SE, et al. Prospective rates of suicide attempts and nonsuicidal self-injury by young people with bipolar disorder participating in a psychotherapy study. *Aust N Z J Psychiatry*. 2016 Feb;50(2):167-73. doi: <http://dx.doi.org/10.1177/0004867415622268>. PMID: 26698820.
250. Rucci P, Frank E, Kostelnik B, et al. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. *Am J Psychiatry*. 2002 Jul;159(7):1160-4. PMID: 12091194.
251. Gonzalez Isasi A, Echeburua E, Liminana JM, et al. Psychoeducation and cognitive-behavioral therapy for patients with refractory bipolar disorder: A 5-year controlled clinical trial. *Eur Psychiatry*. Dec. 2014 March 2014 doi: <http://dx.doi.org/10.1016/j.eurpsy.2012.11.002>. PMID: 23276524.
252. Isasi AG, Echeburua E, Liminana JM, et al. How effective is a psychological intervention program for patients with refractory bipolar disorder? A randomized controlled trial. *J Affect Disord*. 2010 Oct;126(1-2):80-7. doi: <http://dx.doi.org/10.1016/j.jad.2010.03.026>. PMID: 20444503.

253. Miklowitz DJ, Richards JA, George EL, et al. Integrated family and individual therapy for bipolar disorder: results of a treatment development study. *J Clin Psychiatry*. 2003 Feb;64(2):182-91. PMID: 12633127.
254. Todd NJ, Jones SH, Hart A, et al. A web-based self-management intervention for Bipolar Disorder 'living with bipolar': a feasibility randomised controlled trial. *J Affect Disord*. 2014 Dec;169:21-9. doi: 10.1016/j.jad.2014.07.027. PMID: 25129531.
255. Zaretsky A, Lancee W, Miller C, et al. Is cognitive-behavioural therapy more effective than psychoeducation in bipolar disorder? *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2008 Jul;53(7):441-8. PMID: 18674402.
256. Fagiolini A, Frank E, Axelson DA, et al. Enhancing outcomes in patients with bipolar disorder: results from the Bipolar Disorder Center for Pennsylvanians Study. *Bipolar Disord*. 2009 Jun;11(4):382-90. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00700.x>. PMID: 19500091.
257. Faurholt-Jepsen M, Frost M, Ritz C, et al. Daily electronic self-monitoring in bipolar disorder using smartphones - the MONARCA I trial: a randomized, placebo-controlled, single-blind, parallel group trial. *Psychol Med*. 2015 Oct;45(13):2691-704. doi: <http://dx.doi.org/10.1017/S0033291715000410>. PMID: 26220802.
258. Miklowitz DJ, Otto MW, Wisniewski SR, et al. Psychotherapy, symptom outcomes, and role functioning over one year among patients with bipolar disorder. *Psychiatr Serv*. 2006 Jul;57(7):959-65. PMID: 16816280.
259. Deckersbach T, Peters AT, Sylvia L, et al. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *Am J Psychiatry*. 2014 Feb;171(2):178-86. doi: <http://dx.doi.org/10.1176/appi.ajp.2013.13020225>. PMID: 24077657.
260. Miklowitz DJ, Otto MW, Frank E, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *Am J Psychiatry*. 2007 Sep;164(9):1340-7. PMID: 17728418.
261. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Arch Gen Psychiatry*. 2007 Apr;64(4):419-26. PMID: 17404119.
262. Fitzgerald PB, Hoy KE, Elliot D, et al. A negative double-blind controlled trial of sequential bilateral rTMS in the treatment of bipolar depression. *J Affect Disord*. 2016 01 Jul;198:158-62. doi: <http://dx.doi.org/10.1016/j.jad.2016.03.052>. PMID: 27016659 PMID/609157504 Embase.
263. Swartz H, Swanson J. Psychotherapy for bipolar disorder in adults: a review of the evidence. *Focus (Am Psychiatr Publ)*. 2014 Summer;12(3):251-66. doi: 10.1176/appi.focus.12.3.251. PMID: 26279641.
264. Greenhouse WJ, Meyer B, Johnson SL. Coping and medication adherence in bipolar disorder. *J Affect Disord*. 2000 Sep;59(3):237-41. PMID: 10854641.
265. Council NR. The prevention and treatment of missing data in clinical trials: National Academies Press; 2011.
266. Rendell Jennifer M, Gijsman Harm J, Keck Paul K, et al. Olanzapine alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2003.
267. Rendell Jennifer M, Gijsman Harm J, Bauer Mark S, et al. Risperidone alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2006.
268. Burgess Sally SA, Geddes J, Hawton Keith KE, et al. Lithium for maintenance treatment of mood disorders. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2001.
269. Rendell Jennifer M, Geddes J. Risperidone in long-term treatment for bipolar disorder. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2006.
270. Brown R, Taylor Matthew J, Geddes J. Aripiprazole alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2013.

271. Cipriani A, Rendell Jennifer M, Geddes J. Olanzapine in long-term treatment for bipolar disorder. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2009.
272. Cipriani A, Rendell Jennifer M, Geddes J. Haloperidol alone or in combination for acute mania. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2006.
273. Reilly S, Planner C, Gask L, et al. Collaborative care approaches for people with severe mental illness. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2013.
274. Friedman LM, Furberg C, DeMets DL, et al. Fundamentals of clinical trials: Springer; 1998.
275. Sackett DL, Strauss SE, Richardson WS, et al. Evidence-based medicine: how to practice and teach EBM. Edinburgh: Churchill Livingstone; 2000.
276. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol. 2004;19(8):751-60. PMID: 15469032.
277. Amico KR. Percent total attrition: a poor metric for study rigor in hosted intervention designs. Am J Public Health. 2009 Sep;99(9):1567-75. doi: 10.2105/ajph.2008.134767. PMID: 19608965.
278. Sen S, Prabhu M. Reporting bias in industry-supported medication trials presented at the American Psychiatric Association meeting. J Clin Psychopharmacol. 2012 Jun;32(3):435. doi: <https://dx.doi.org/10.1097/JCP.0b013e318253d737>. PMID: 22561482.
279. Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med. 2008 Jan 17;358(3):252-60. doi: <https://dx.doi.org/10.1056/NEJMsa065779>. PMID: 18199864.
280. Turner EH, Kneopflmacher D, Shapley L. Publication bias in antipsychotic trials: an analysis of efficacy comparing the published literature to the US Food and Drug Administration database. PLoS Medicine / Public Library of Science. 2012;9(3):e1001189. doi: <https://dx.doi.org/10.1371/journal.pmed.1001189>. PMID: 22448149.
281. Driessen E, Hollon SD, Bockting CL, et al. Does Publication Bias Inflate the Apparent Efficacy of Psychological Treatment for Major Depressive Disorder? A Systematic Review and Meta-Analysis of US National Institutes of Health-Funded Trials. PLoS ONE [Electronic Resource]. 2015;10(9):e0137864. doi: <https://dx.doi.org/10.1371/journal.pone.0137864>. PMID: 26422604.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
BD	Bipolar Disorder
BPD	Borderline Personality Disorder
C	Comparison
CBT	Cognitive Behavioral Therapy
CCMD-3	Chinese Classification and Diagnosis Criteria of Mental Disorder, 3 rd Version
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative Effectiveness Review
CGI	Clinical Global Impression
CGI-BP	Clinical Global Impressions-Bipolar Questionnaire
CGI-BP-S	Clinical Global Impressions-Bipolar Questionnaire Severity Subscale
CGI-I	Clinical Global Impressions-Improvement
CI	Confidence Interval
DSM	Diagnostic Statistical Manual of Mental Disorders
DSS	Depressive Syndrome Scale
ECT	Electroconvulsive Therapy
ER	Extended Release
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
FPI	Family or Partner Interventions
FTP	Family Therapy Plus Pharmacotherapy
GAS	Global Assessment Scale
HAM-D	Hamilton Scale for Depression
HDRS	Hamilton Depression Rating Scale
I	Intervention
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10 th Revision
ICTRP	International Controlled Trials Registry Platform
IDS-C	Inventory of Depressive Symptoms (Clinician-rated)
IPSRT	Interpersonal and Social Rhythm Therapy
KSADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
KQ	Key Question
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at Random
MD	Mean Difference
MDQ	Mood Disorder Questionnaire
MIDs	Minimum Important Differences
MINI	MINI International Neuropsychiatric Interview
NA	Not Applicable

NOS	Not Otherwise Specified
NR	Not Reported
NRC	National Research Council
OR	Odds Ratio
PICOTS	Populations, Interventions, Comparisons, Outcomes, Timing, and Setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
REML	Restricted Maximum Likelihood Estimator
ROB	Risk of Bias
RTI	Research Triangle Institute
SADS-C	Schedule for Affective Disorders and Schizophrenia, change version
SCID-I	Structured Clinical Interview for the DSM-IV Axis I Disorders
SE	Standard Error
SIPs	Scientific Information Packets
SMD	Standardized Mean Differences
SOE	Strength of Evidence
STEP-BD	Bipolar Disorder Systematic Treatment Enhancement Program
TEP	Technical Expert Panel
WHOQOL-BREF	World Health Organization Quality of Life–Short Version
WMD	Weighted Mean Differences
YMRS	Young Mania Rating Scale

Appendix A. Search Strategies

Database: Ovid MEDLINE(R)

Search Strategy: RCTs

```
1      meta analysis as topic/ (13510)
2      meta-analy$.tw. (52680)
3      metaanaly$.tw. (1203)
4      meta-analysis/ (45541)
5      (systematic adj (review$1 or overview$1)).tw. (43341)
6      exp Review Literature as Topic/ (7347)
7      or/1-6 (104864)
8      cochrane.ab. (25132)
9      embase.ab. (23427)
10     (psychlit or psyclit).ab. (849)
11     (psychinfo or psycinfo).ab. (8872)
12     or/8-11 (39709)
13     reference list$.ab. (8541)
14     bibliograph$.ab. (10454)
15     hand search.ab. (775)
16     relevant journals.ab. (639)
17     manual search$.ab. (2034)
18     or/13-17 (20943)
19     selection criteria.ab. (18005)
20     (data adj2 (extract* or abstract*)).ab. (26471)
21     19 or 20 (37021)
22     review/ (1843638)
23     21 and 22 (21523)
24     Comment/ (528055)
25     Letter/ (802670)
26     editorial/ (333012)
27     animal/ (5241748)
28     human/ (13252793)
29     27 not (28 and 27) (3807921)
30     or/24-26,29 (4993696)
31     7 or 12 or 18 or 23 (130774)
32     31 not 30 (122020)
33     randomized controlled trials as topic/ (90815)
34     randomized controlled trial/ (366322)
35     random allocation/ (79441)
36     double blind method/ (124067)
37     single blind method/ (18635)
38     clinical trial/ (484436)
```

39 clinical trial, phase i.pt. (13833)
40 clinical trial, phase ii.pt. (22208)
41 clinical trial, phase iii.pt. (8628)
42 clinical trial, phase iv.pt. (905)
43 controlled clinical trial.pt. (87769)
44 randomized controlled trial.pt. (366322)
45 multicenter study.pt. (167455)
46 clinical trial.pt. (484436)
47 exp clinical trials as topic/ (276232)
48 or/33-47 (1007391)
49 (clinical adj trial\$.tw. (193529)
50 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (121456)
51 placebos/ (32313)
52 placebo\$.tw. (148340)
53 randomly allocated.tw. (15301)
54 (allocated adj2 random\$).tw. (17733)
55 or/49-54 (386436)
56 48 or 55 (1124628)
57 case report.tw. (180193)
58 case report.tw. (180193)
59 letter/ (802670)
60 historical article/ (298584)
61 or/57-60 (1270322)
62 56 not 61 (1095429)
63 exp cohort studies/ (1320622)
64 cohort\$.tw. (244490)
65 controlled clinical trial.pt. (87769)
66 epidemiological methods/ (29547)
67 limit 66 to yr=1971-1983 (5333)
68 or/63-65,67 (1486088)
69 (ae or to or po or co).fs. (3071650)
70 side effect\$.ti,ab. (162368)
71 side effect\$.ti,ab. (162368)
72 ((adverse or undesireable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or
event\$ or outcome\$)).ti,ab. (277104)
73 exp product surveillance, postmarketing/ (10888)
74 exp adverse drug reaction reporting systems/ (5477)
75 exp clinical trials, phase iv/ (221)
76 exp poisoning/ (129396)
77 exp substance-related disorders/ (220844)
78 exp drug toxicity/ (86909)
79 exp abnormalities, drug induced/ (13732)
80 exp drug monitoring/ (13980)
81 exp drug hypersensitivity/ (37576)

82 (toxicity or complication\$ or noxious or tolerability).ti,ab. (807144)
 83 exp postoperative complication/ (410502)
 84 exp intraoperative complications/ (39444)
 85 or/69-84 (4065205)
 86 exp Bipolar disorder/ (30924)
 87 bipolar*.ti. (15477)
 88 cyclothymia.ti. (77)
 89 (rapid adj cycl*).ti. (416)
 90 (mania or hypomania or manic or hypomanic).ti. (5588)
 91 or/86-90 (35187)
 92 32 and 91 (799)
 93 62 and 91 (4169)
 94 68 and 85 and 91 (1916)
 95 limit 92 to yr="1994-Current" (788)
 96 limit 93 to yr="1994-Current" (3286) RCTs
 97 limit 94 to yr="1994-Current" (1518)
 98 95 not 96 (522) Systematic reviews
 99 97 not (95 or 96) (989) Cohort harms
 100 (68 and 91) not 85 (3060)
 101 limit 100 to yr="1994-Current" (2188) Cohort benefits
 102 101 not (95 or 96 or 97) (1704)
 103 limit 96 to "all child (0 to 18 years)" (726)
 104 limit 96 to "all adult (19 plus years)" (2056)
 105 103 and 104 (474)
 106 103 not 105 (252)
 107 96 not 106 (3034) RCTs without pediatric-only
 108 limit 98 to "all child (0 to 18 years)" (70)
 109 limit 98 to "all adult (19 plus years)" (161)
 110 108 and 109 (46)
 111 108 not 110 (24)
 112 98 not 111 (498) Systematic reviews without pediatric-only
 113 limit 99 to "all child (0 to 18 years)" (274)
 114 limit 99 to "all adult (19 plus years)" (843)
 115 113 and 114 (208)
 116 113 not 115 (66)
 117 99 not 116 (923) Cohort harms without pediatric-only
 118 limit 102 to "all child (0 to 18 years)" (607)
 119 limit 102 to "all adult (19 plus years)" (1360)
 120 118 and 119 (459)
 121 118 not 120 (148)
 122 102 not 121 (1556) Cohort benefits without pediatric-only
 123 (resection or prostate or radiofrequency or sealer or ablation or hip or fibrillation).ab.
 (396573)
 124 107 not 123 (2855) RCTs without pediatric-only or resection, ablation, etc.

- 125 112 not 123 (495) Systematic reviews without pediatric-only or resection, ablation, etc.
 126 117 not 123 (800) Cohort harms without pediatric-only or resection, ablation, etc.
 127 122 not 123 (1515) Cohort benefits without pediatric-only or resection, ablation, etc.

Database: Embase Classic+Embase

- 1 retracted article/ (6992)
 2 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (964464)
 3 (animal\$ not human\$).sh,hw. (3892889)
 4 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (4026686)
 5 1 or 2 (971306)
 6 5 not (3 or 4) (788381)
 7 exp cohort analysis/ (159852)
 8 exp longitudinal study/ (65122)
 9 exp prospective study/ (251233)
 10 exp follow up/ (749090)
 11 cohort\$.tw. (363883)
 12 7 or 8 or 9 or 10 or 11 (1281760)
 13 exp case-control study/ (90165)
 14 (case\$ and control\$).tw. (421076)
 15 13 or 14 (455349)
 16 (case\$ and series).tw. (156704)
 17 exp review/ (2051725)
 18 (literature adj3 review\$).ti,ab. (210224)
 19 exp meta analysis/ (76123)
 20 exp "Systematic Review"/ (64783)
 21 17 or 18 or 19 or 20 (2235229)
 22 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab. (99517)
 23 retracted article/ (6992)
 24 22 or 23 (106462)
 25 21 and 24 (78850)
 26 (systematic\$ adj2 (review\$ or overview)).ti,ab. (66304)
 27 (meta?anal\$ or meta anal\$ or metaanal\$ or metanal\$).ti,ab. (75185)
 28 25 or 26 or 27 (159362)
 29 (ae or si or to or co).fs. (3025512)
 30 (safe or safety).ti,ab. (597602)
 31 side effect\$.ti,ab. (238444)

32 ((adverse or undesirable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or outcome\$)).ti,ab.
 (406794)
 33 exp adverse drug reaction/ (358463)
 34 exp drug toxicity/ (77722)
 35 exp intoxication/ (328776)
 36 exp drug safety/ (221042)
 37 exp drug monitoring/ (40454)
 38 exp drug hypersensitivity/ (49258)
 39 exp postmarketing surveillance/ (22410)
 40 exp phase iv clinical trial/ (1496)
 41 (toxicity or complication\$ or noxious or tolerability).ti,ab. (1146485)
 42 exp postoperative complication/ (478856)
 43 exp peroperative complication/ (19583)
 44 or/29-43 (4747913)
 45 exp *bipolar disorder/ (21744)
 46 (manic and depress*).ti. (2122)
 47 (bipolar and (disorder or depress*)).ti. (14239)
 48 45 or 46 or 47 (25031)
 49 28 and 48 (966)
 50 49 not (3 or 4) (463)
 51 limit 50 to yr="2010 -Current" (238)
 52 limit 51 to (book or conference abstract or conference proceeding or "conference review" or editorial or erratum or letter or note or short survey or trade journal) (105)
 53 51 not 52 (133) Systematic Reviews
 54 6 and 48 (1987)
 55 54 not 52 (1952) RCTs
 56 12 and 48 (2527)
 57 56 not (3 or 4) (2224)
 58 57 not 51 (2195)
 59 44 and 48 (5891)
 60 58 and 59 (417) Cohort Harms

Database: PsycINFO

Search Strategy: RCTs

- 1 retracted article/ (6992)
- 2 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (964464)
- 3 (animal\$ not human\$).sh,hw. (3892889)
- 4 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ (4026686)
- 5 1 or 2 (971306)
- 6 5 not (3 or 4) (788381)
- 7 exp cohort analysis/ (159852)
- 8 exp longitudinal study/ (65122)
- 9 exp prospective study/ (251233)
- 10 exp follow up/ (749090)
- 11 8 cohort\$.tw. (363883)
- 12 9 7 or 8 or 9 or 10 or 11 (1281760)
- 13 exp case-control study/ (90165)
- 14 10 (case\$ and control\$).tw. (421076)
- 15 13 or 14 (455349)
- 16 11 (case\$ and series).tw. (156704)
- 17 12 exp review/ (2051725)
- 18 13 (literature adj3 review\$).ti,ab. (210224)
- 19 14 exp meta analysis/ (76123)
- 20 exp "Systematic Review"/ (64783)
- 21 15 12 or 13 or 14 (2235229)
- 22 16 (medline or embase or pubmed or cinahl or amed or psychlit or psychinfo or scisearch or cochrane).ti,ab. (99517)
- 23 17 retracted article/ (6992)
- 24 18 16 or 17 (106462)
- 25 19 15 and 18 (78850)
- 26 20 (systematic\$ adj2 (review\$ or overview)).ti,ab. (66304)
- 27 21 (meta?anal\$ or meta anal\$ or metaanal\$ or metanal\$).ti,ab. (75185)
- 28 22 19 or 20 or 21 (159362)
- 29 (ae or si or to or co).fs. (3025512)
- 30 23 (safe or safety).ti,ab. (597602)
- 31 24 side effect\$.ti,ab. (238444)
- 32 25 ((adverse or undesirable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or outcome\$)).ti,ab. (406794)
- 33 exp adverse drug reaction/ (358463)
- 34 exp drug toxicity/ (77722)
- 35 26 exp intoxication/ (328776)
- 36 exp drug safety/ (221042)

37 exp drug monitoring/ (40454)
 38 exp drug hypersensitivity/ (49258)
 39 exp postmarketing surveillance/ (22410)
 40 exp phase iv clinical trial/ (1496)
 41 27 (toxicity or complication\$ or noxious or tolerability).ti,ab. (1146485)
 42 exp postoperative complication/ (478856)
 43 exp peroperative complication/ (19583)
 44 28 or/23-27(4747913)
 45 29 exp *bipolar disorder/ (21744)
 46 30 (manic and depress*).ti. (2122)
 47 31 (bipolar and (disorder or depress*)).ti. (14239)
 48 32 29 or 30 or 31 (25031)
 49 33 22 and 32 (966)
 50 34 33 not (3 or 4) (463)
 51 35 limit 34 to yr="2015" (238)
 52 36 limit 35 to (book or conference abstract or conference proceeding or "conference review"
 or editorial or erratum
 or letter or note or short survey or trade journal) (105)
 53 37 35 not 36 (133) Systematic Reviews
 54 38 6 and 32 (1987)
 55 39 38 not 36 (1952) RCTs
 56 40 9 and 32 (2527)
 57 41 40 not (3 or 4) (2224)
 58 42 41 not 35 (2195)
 59 43 28 and 32 (5891)
 60 44 42 and 43 (417) Cohort Harms

Appendix B. Risk of Bias Assessment Tool

Question	Response	Criteria	Justification
Internal Validity			
1. Is the study design prospective, retrospective, or mixed?	Prospective <input type="checkbox"/>	Outcome has not occurred at the time the study is initiated and information is collected over time to assess relationships with the outcome.	
	Mixed <input type="checkbox"/>	Studies in which one group is studied prospectively and the other retrospectively.	
	Retrospective <input type="checkbox"/>	Analyzes data from past records.	
2. Are inclusion/exclusion criteria clearly stated?	Yes <input type="checkbox"/>		
	Partially <input type="checkbox"/>	Some, but not all, criteria stated or some not clearly stated.	
	No <input type="checkbox"/>		
3. Are baseline characteristics measured using valid and reliable measures and equivalent in both groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
4. Is the level of detail describing the intervention adequate?	Yes <input type="checkbox"/>	Intervention described included adequate service details	
	Partially <input type="checkbox"/>	Some of the above features.	
	No <input type="checkbox"/>	None of the above features.	
5. Is the selection of the comparison group appropriate?	Yes <input type="checkbox"/>	Considering bipolar type, diagnostic assessment, other patient characteristics	
6. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results?	Yes <input type="checkbox"/>	Accounted for concurrent informal care.	
	Partially <input type="checkbox"/>		
	No <input type="checkbox"/>		
7. Any attempt to balance the allocation between the groups (e.g. stratification, matching, propensity scores)?	Yes <input type="checkbox"/>	(if yes, what was used?)	
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
8. Were outcomes assessors blinded?	<input type="checkbox"/>	Who were outcome assessors?	
9. Are outcomes assessed using valid and reliable measures, implemented consistently across	Yes <input type="checkbox"/>	Measure valid and reliable (i.e. objective measures, well validated scale, provider report); and equivalent across groups.	
	Partially <input type="checkbox"/>	Some of the above features (partially validated scale)	

Question	Response	Criteria	Justification
all study participants?	No <input type="checkbox"/>	None of the above features. (self-report, scales with lower validity, reliability); not equivalent across groups	
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
10. Is the length of follow-up the same for all groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
11. Did attrition result in a difference in group characteristics between baseline and follow-up?	Yes <input type="checkbox"/>	(measurement period of interest if repeated measures)	
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
12. If baseline characteristics are not similar, does the analysis control for baseline differences between groups?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
13. Are confounding and/or effect modifying variables assessed using valid and reliable measures across all study participants?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained (i.e. retrospective designs where eligible at baseline could not be determined)	
	NA <input type="checkbox"/>	No confounders or effect modifiers included in the study.	
14. Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g. through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?	Yes <input type="checkbox"/>		
	Partially <input type="checkbox"/>	Some variables taken into account or adjustment achieved to some extent.	
	No <input type="checkbox"/>	Not accounted for or not identified.	
	Uncertain <input type="checkbox"/>	Could not be ascertained	
15. Are the statistical methods used to	Yes <input type="checkbox"/>	Statistical techniques used must be appropriate to the data.	

Question	Response	Criteria	Justification
assess the primary outcomes appropriate to the data?	Partially <input type="checkbox"/>		
	No <input type="checkbox"/>		
	Uncertain <input type="checkbox"/>	Could not be ascertained	
16. Are reports of the study free of suggestion of selective outcome reporting?	Yes <input type="checkbox"/>		
	No <input type="checkbox"/>	Not all prespecified outcomes reported, subscales not prespecified reported, outcomes reported incompletely.	
	Uncertain <input type="checkbox"/>	Could not be ascertained.	
17. Funding source identified	No <input type="checkbox"/>		Industry, government, university, Foundation (funded by what money source?)
	Yes <input type="checkbox"/>	Who provided funding?	
	Uncertain <input type="checkbox"/>		
	Overall Assessment		
18. Overall Risk of Bias assessment	Low <input type="checkbox"/>	Results are believable taking study limitations into consideration	
	Moderate <input type="checkbox"/>	Results are probably believable taking study limitations into consideration	
	High <input type="checkbox"/>	Results are uncertain taking study limitations into consideration	

Appendix C. Outcomes

Appendix Table C1. Outcomes used in bipolar treatment studies

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Altman Self Rating Mania Scale (ASRM)			Altman EG, Hedeker D, Peterson JL, Davis JM: The Altman Self-Rating Mania Scale. <i>Biol Psychiatry</i> 1997, 42:948-955.
Beck Anxiety Inventory (BAI)			Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. <i>J Consult Clin Psychol</i> . 1988;56(6):893-897.
Beck Depression Inventory (BDI)	BDI		Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. <i>Arch Gen Psychiatry</i> . 1961;4(6):561-571.
	BDI-II		Beck AT, Steer RA, Brown GK. Manual for Beck Depression Inventory II (BDI-II). San Antonio, TX: Psychological Corp; 1996.
Beck Scale for Suicide Ideation			
Bipolar Self-efficacy Scale			Centre for Clinical Interventions (2008) Bipolar Self Efficacy Scale. Centre for Clinical Interventions, Perth, Australia.
Brief Psychiatric Rating Scale (BPRS)			Overall J, Gorham D. The brief psychiatric rating scale. <i>Psychol Rep</i> 1962; 10: 799–812.
Brief Symptom Inventory (BSI)			Beurs E de, Zitman FG: De Brief Symptom Inventory (BSI): De betrouwbaarheid en validiteit van een handzaam alternatief voor de SCL-90. <i>Maandblad Geestelijke Volksgezondheid</i> 2006, 61:120-141.
Clinical Global Impressions	CGI	Minimally important difference: 1 point	Lukasiewicz et al. Young mania rating scale: how to interpret the numbers? <i>International Journal of Methods in Psychiatric Research</i> . <i>Int. J. Methods Psychiatr. Res.</i> 22(1): 46–58 (2013). DOI: 10.1002/mpr.1379
	Scale for Bipolar Disorder (CGI-BP)	mania score only (20728318)	Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
	Bipolar disorder-Severity (CGI-BP-S)	mania score only (18835043)	illness (BP): the CGI-BP. <i>Psychiatry Res</i> 1997; 73:159-171.
	Severity of Illness Scale (CGI-S)		Guy, W. (Ed.), 1976. ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. US Department of Health, Education, and Welfare, Washington, DC, pp. 218–222
	Improvement scale (CGI-I)		
	Change scale (CGI-C)		
Functioning Assessment Short Test			Rosa AR, Sánchez-Moreno J, Martínez-Arán A, Salamero M, Torrent C, Reinares M, Comes M, Colom F, Van Riel W, Ayuso-Mateos JL, Kapczinski F, Vieta E: Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. <i>Clin Pract Epidemiol Ment Health</i> 2007; 3:5
Global Assessment of Functioning			Diagnostic and Statistical Manual of Mental Disorders—Text Revision (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Association; 2000.
Hamilton Anxiety Rating Scale (HARS)			Hamilton M. The assessment of anxiety states by rating. <i>Br J Med Psychol.</i> 1959;32(1):50-55.
Hamilton Depression Rating Scale	HAM-D (also referred to as HDRS)		Hamilton, M., 1960. A rating scale for depression. <i>J. Neurol. Neurosurg. Psychiatry</i> 3, 62–66.
	HAMD-17		
	HSRD-25		Thase ME, Carpenter L, Kupfer DJ, Frank EF. Clinical significance of reversed vegetative subtypes of recurrent major depression. <i>Psychopharmacol Bull</i> 1991; 27: 17–22.

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
	HAMD-28	"with embedded 'typical' HAM-D 17 and 'atypical' HAM-D 17-R symptom cores" (18486235); Proportion of responders with a >50% reduction in baseline HAM-D (18486235); Proportion of remitters with a final HAM-D score <=8 (18486235)	Williams, J.B.W., 1988. A structured interview guide for the Hamilton Depression Rating Scale. Arch. Gen. Psychiatry 45, 742–747. Reimherr, F.W., Amsterdam, J.D., Fawcett, J., Quitkin, F.M., Rosenbaum, J., Beasley, C., Michelson, D., Roback, P., Sundell, K., 1998. Optimal length of continuation therapy: a prospective assessment during fluoxetine long-term treatment. Am. J. Psychiatry 55, 1247–1253.
Inventory for Depressive Symptomology (IDS)			Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996; 26:477-486.
Life Chart Method (NIMH-LCM)			Denicoff KD, Leverich GS, Nolen WA, Rush AJ, McElroy SL, Keck PE, et al: Validation of the prospective NIMH-Life-Chart Method (NIMH-LCM-p) for longitudinal assessment of bipolar illness. Psychol Med 2000, 30:1391-1397.
Longitudinal Interval Follow-up Evaluation			Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540-548.
Montgomery-Asberg Depression Rating Scale (MADRS)		Individual item scores (22868059)	Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.
Positive and Negative Syndrome Scale (PANSS)		Cognitive and Hostility subscales (18835043)	Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale for schizophrenia. Schizophr. Bull. 13, 261–276.
Quality of Life, Enjoyment, and Satisfaction Questionnaire			Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993; 29:321-326.

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Quality of Life Scale of the World Health Organization Quality of Life Assessment	WHOQOL-BREF		Fleck MP, Louzada S, Xavier M et al. Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref. Rev Saude Publica 2000;34:178–183.
Quick Inventory of Depressive Symptoms (QIDS)	Self-report (QIDS-SR)		Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54:573-583.
Rathus Assertiveness Schedule (RAS)			Rathus, S.A., 1973. A 30 item schedule for assessing assertiveness. Behavior Therapy 4, 398–406.
Sheehan Disability Scale (SDS)			In Sheehan DV. <i>The Anxiety Disease</i> . New York, NY: Charles Scribner; 1983:151.
Short-Form Health Survey	SF-12v2		Ware J. (1994) SF-36 Health Survey Manual and Interpretation Guide. The Health Institute, Boston, MA.
Social Adjustment Scale Self Report (SAS-SR)			Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–1115.
STEP-BD Clinical Monitoring Form			Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord. 2002;4:323-327.
STEP-BD Affective Disorders Evaluation			Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry. 2003;53:1028-1042.
Symptom Check List	SCL-90	Used only depression and mania subscales (22070452)	Derogatis L. & Cleary P. (1977) Confirmation of the dimensional structure of the SCL-90: a study in construct validation. Journal of Clinical Psychology 33, 981–989.

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Young Mania Rating Scale	YMRS	Proportion of patients with YMRS ≥ 8 at any time during treatment (23609385) Individual item scores (22868059, 22134043)	Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 61, 638–642.
		Minimally important difference: 6 points	Lukasiewicz et al. Young mania rating scale: how to interpret the numbers? International Journal of Methods in Psychiatric Research. Int. J. Methods Psychiatr. Res. 22(1): 46–58 (2013). DOI: 10.1002/mpr.1379
Change in mood status		"Participants had syndromal or subsyndromal depressive symptoms, as defined in the DSM-IV-TR or STEP-BD, respectively. Subsyndromal symptoms consisted of having >2 pervasive DSM-IV-TR depressive symptoms but not meeting criteria for a DSM-IV-TR syndromal depressive, hypomanic, manic, or mixed episode" (21318192)	

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Relapse		<p>“(1) a YMRS score higher than 14 or a MADRS score higher than 15; (2) 20% or greater increase in the YMRS or MADRS scores from the previous study visit for patients with a MADRS score of 10 or higher or a YMRS score of 8 or higher at the current study visit; (3) urgent care visit/referral (psychiatric hospitalization; emergency department visit; or referral for respite care, partial hospitalization, or intensive outpatient treatment) due to worsening mood symptoms; (4) a Clinical Global Impression—Severity of Illness score of 4 or higher; (5) syndromal relapse (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria for manic, hypomanic, major depressive, or mixed episode met); (6) withdrawal from the study due to inefficacy; and (7) necessary clinical medication adjustments (NCAs) [change in medication treatment intended to prevent worsening of clinical symptoms, and included addition of a new mood stabilizer, antipsychotic, or antidepressant [other than the experimental treatment]; substitution of an existing bipolar medication with a new drug; and/or a 20% or greater change in dose of any current medication (excluding routine increases in dose due to titration).].” (22104634)</p> <p>“Relapse or recurrence of a manic or depressive episode defined as a score ≥ 4 (at least moderate symptoms) on the CGI-BP severity of depression or mania scale” (21320258)</p>	

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
First recurrence of any mood symptoms		<p>“YMRS ≥ 15 and Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S) for Mania ≥ 4; YMRS < 15, MADRS ≥ 16 and CGI-BP-S for depression ≥ 4; voluntary or involuntary hospitalization for any mood symptoms; therapeutic intervention to prevent or treat an impending mood episode (i.e., use of benzodiazepines for >3 consecutive days; supplementation with an antipsychotic, antidepressant, or mood stabilizer; another therapeutic measure [e.g., psychotherapy or electroconvulsive therapy]); any other clinically relevant event suggestive of a recurrent mood episode.” (22377512)</p> <p>“ITT analysis of the prevalence . . . of mood symptoms (comparing any depressive or manic symptoms vs. none over the first year)” (20409444)</p>	
Time to recurrence		<p>“time (days) elapsed between baseline and the emergence of a new acute episode according to DSM-IV criteria and scores above or equal to 20 on the YMRS for manic recurrence; above or equal to 12 for hypomanic recurrence; above or equal to 17 on the HRSD-17 for depressive recurrence; and above or equal to 20 on the YMRS and 12 on the HRSD-17 for mixed recurrence.” (19252157)</p> <p>“any of the following: 1) fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; 2) required treatment intervention with any mood stabilizer, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; 3) hospitalization for any bipolar mood episode; 4) had YMRS score >12, Montgomery Åsberg Depression Rating Scale (MADRS) score >12, or CGI-S scale score >4 at any visit; or 5) needed an increase in risperidone LAI dosage or supplementation with oral risperidone”. (20227682)</p> <p>Weeks to first new episode, weeks to first depressive episode, weeks to first manic episode (20409444)</p>	
Number of recurrences		See “time to recurrence” definition for 19252157	
Time spent ill		Prospectively measured number of days participants met criteria listed under “time to recurrence” for 19252157	

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Emergent depression		MADRS Total score ≥ 18 and ≥ 4 point increase from baseline for any two consecutive assessments (18835043)	
Full syndromal depressive relapse		Increase in baseline HAM-D score to ≥ 14 and met criteria for a major depressive episode (20360317)	Reimherr FW, Amsterdam JD, Quitkin FM, Rosenbaum JF, Fava M, Zajecka J, Beasley DM Jr, Michelson D, Roback P, Sundell K: Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am J Psychiatry 1998; 155:1247–1253
Severe depressive symptoms		BDI score > 18	
Subsyndromal depressive episode		Any increase in baseline HAM-D score without meeting criteria for major depressive episode (20360317)	
Switch to depressive symptoms		HAMD-17 ≥ 13 in patients with HAMD-17 ≤ 7 at baseline (22134043)	
Time to first recurrence of depressive symptoms		YMRS < 15 , MADRS ≥ 16 and CGI-BP-S for depression ≥ 4 (22377512) “how long the MADRS score was maintained at $< 50\%$ of its baseline value after patients reached this level for the first time during phase 1 or 2.” (21320258)	
Hypomania		DSM-IV criteria: episode lasting ≥ 4 days with ≥ 4 symptoms (20360317, 23609385); YMRS score cut-points of ≥ 8 and ≥ 12 at any study visit (20360317)	
Moderate mania		YMRS > 6	
Remission of manic symptoms		YMRS ≤ 12 (22134043)	
Subsyndromal hypomania		Episode lasting ≤ 3 days with ≥ 4 symptoms (20360317, 23609385) Episode lasting ≥ 4 days with ≤ 3 symptoms (20360317, 23609385) Episode lasting ≤ 3 days with ≤ 3 symptoms (23609385)	
Switch to mania/hypomania		"Need to discontinue antidepressant medication because of the emergence of manic symptoms" (19358785)	

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
Time to first recurrence of manic symptoms		YMRS ≥ 15 and Clinical Global Impression-Bipolar Disorder-Severity of Illness Scale (CGI-BP-S) for Mania ≥ 4 (22377512)	
Adherence to treatment		<p>"Adherence was assessed by the combination of an adherence-focused interview with the individual, an adherence-focused interview with significant first-degree relatives or a partner and by analyses of plasma concentrations of mood stabilisers" (19252157)</p> <p>"Adherence with study medication was evaluated with returned capsule count. Patients who missed ≥ 5 consecutive days of study medication were considered nonadherent and discontinued from the trial." (20361901)</p>	Fully described in Simon GE, Ludman EJ, Bauer MS, Unutzer J, Operskalski B. Long-term effectiveness and cost of a systematic care program for bipolar disorder. Arch Gen Psychiatry 2006; 63: 500–8.
Hospitalizations		Hospitalized "owing to recurrence" (19252157)	
Necessary clinical adjustments		<p>"a proxy for the clinical burden of a treatment strategy and capture the treatment changes that result from lack of efficacy or safety issues. They consist of all medication adjustments necessary to respond to clinical need, such as exacerbation of mood symptoms, emergence of a mood episode, persistence of symptoms, or adjustments because of adverse effects. Necessary clinical adjustments do not include planned dosage titrations or decreases in dosage based on the assessment of positive responses or the judgment that a medication is no longer required" (23288387)</p>	Nierenberg AA, Sylvia LG, Leon AC, Reilly-Harrington NA, Ketter TA, Calabrese JR, Thase ME, Bowden CL, Friedman ES, Ostacher MJ, Novak L, Iosifescu DV; Litmus Study Group: Lithium Treatment Moderate-Dose Use Study (LiTMUS) for bipolar disorder: rationale and design. Clin Trials 2009; 6:637–648
Response to treatment	Positive	<p>50%+ improvement on IDS from baseline <i>or</i> 2+ point decrease in CGI-BP from baseline (19358785)</p> <p>$\geq 50\%$ reduction in total HAMD-17 <i>and</i> final HAMD-17 score ≥ 9 at treatment week 10 (23609385)</p> <p>$\geq 50\%$ reduction from baseline in YMRS <i>and</i> MADRS (22868059)</p> <p>$\geq 50\%$ reduction from baseline in YMRS (20947174, 22377512, 20624657, 22134043, 20361901, 20728318, 18835043)</p> <p>50%+ improvement on HDRS, BDI, QIDS-SR, <i>or</i> CGI-I (22579164)</p> <p>$\geq 50\%$ change in HDRS score (22213770)</p> <p>CGI-BP improvement of depression score of 1 or 2 (very much improved or much improved) (21320258)</p>	

Outcome/measure	Version (if applicable)	Operationalization (other than total score, if applicable)	Source
	Partial	Pt judged partial improvement, but did not meet criteria for "positive response" (19358785)	
	Nonresponse	<50% reduction in HAMD-17 by treatment week 10 (23609385) Exiting study <i>or</i> <50% improvement on HDRS (22213770)	
Remission		IDS < 12 OR CGI-BP depression severity of 1 (19358785) >=50% reduction in total HAMD-17 <i>and</i> final HAMD-17 score <=8 at treatment week 6, 8, or 10, maintained for 2 weeks (23609385) YMRS <=12 <i>and</i> HAMD-17 <=7 (22134043) YMRS <=12 <i>and</i> MADRS <=10 (22868059) YMRS <=12 <i>and</i> MADRS <=12 (22377512) YMRS <=12 (20947174, 20624657, 18835043) CGI-I outcome "remission", HDRS <=7, QIDS-SR <=5, <i>or</i> BDI <=9 (22579164) HDRS<8 (22213770) CGI-BP-S<2 (23288387)	
Laboratory tests		Serum Lithium levels (23288387)	
Time to early discontinuation from study medication		"Time to early discontinuation from study medication for any reason (including recurrence), before termination of the study when at least 114 recurrences were observed, was also analyzed."	
Time to onset of therapeutic effect		"the first time point at which [the treatment group] was statistically significantly different from the [comparison treatment] for the change from baseline in the YMRS total score and remained different thereafter until endpoint" (20947174, 20624657)	

Appendix D. Excluded References

Excluded References¹⁻⁹⁵⁷

1. Aarre TF, Dahl AA. Pharmacotherapy for bipolar depression: A review of the evidence. *Current Psychiatry Reviews*. 2008 2008;4(3):145-56. doi: <http://dx.doi.org/10.2174/157340008785829913>. **Ineligible study design**
2. Agosti V, Stewart JW. Efficacy and safety of antidepressant monotherapy in the treatment of bipolar-II depression. *International Clinical Psychopharmacology*. 2007 Sep;22(5):309-11. PMID: 17690600 **Ineligible study design**
3. Akhondzadeh S, Mohajeri H, Reza Mohammadi M, et al. Risperidone as an adjunct to lithium and haloperidol for the treatment of medication-naïve patients with acute mania: a double blind and placebo controlled trial. *BMC Psychiatry*. 2003 Jun 19;3:7. PMID: 12816549 **Bipolar not analyzed separately**
4. Akiskal HS, Akiskal KK, Lancrenon S, et al. Validating the soft bipolar spectrum in the French National EPIDEP Study: the prominence of BP-II 1/2. *Journal of Affective Disorders*. 2006 Dec;96(3):207-13. PMID: 16647762 **Ineligible study design**
5. Albert U, Maina G, Aguglia A, et al. Vagus nerve stimulation for treatment-resistant mood disorders: a long-term naturalistic study. *BMC Psychiatry*. 2015 Mar 31;15:64. doi: <https://dx.doi.org/10.1186/s12888-015-0435-8>. PMID: 25884606 **Less than 11 subjects per arm**
6. Alda M, McKinnon M, Blagdon R, et al. Methylene blue treatment for residual symptoms of bipolar disorder: Randomised crossover study. *British Journal of Psychiatry*. 2017 January;210(1):54-60. doi: <http://dx.doi.org/10.1192/bjp.bp.115.173930>. PMID: 614051189 **Ineligible intervention**
7. Allan SJ, Kavanagh GM, Herd RM, et al. The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial. *British Journal of Dermatology*. 2004 May;150(5):966-9. PMID: 15149510 **Not bipolar disorder**
8. Allen MH, Hirschfeld RM, Wozniak PJ, et al. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. *American Journal of Psychiatry*. 2006 Feb;163(2):272-5. PMID: 16449481 **No eligible outcomes reported**
9. Altinbas K, Ozerdem A, Prieto ML, et al. A multinational study to pilot the modified Hypomania Checklist (mHCL) in the assessment of mixed depression. *Journal of Affective Disorders*. 2014 Jan;152-154:478-82. doi: <http://dx.doi.org/10.1016/j.jad.2013.07.032>. PMID: 24070907 **Ineligible study design**
10. Altshuler LL, Frye MA, Gitlin MJ. Acceleration and augmentation strategies for treating bipolar depression. *Biological Psychiatry*. 2003 Apr 15;53(8):691-700. PMID: 12706955 **Ineligible study design**
11. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. *American Journal of Psychiatry*. 2006 Feb;163(2):313-5. PMID: 16449487 **No eligible outcomes reported**

12. Amann B, Born C, Crespo JM, et al. Lamotrigine: when and where does it act in affective disorders? A systematic review. *Journal of Psychopharmacology*. 2011 Oct;25(10):1289-94. doi: <http://dx.doi.org/10.1177/0269881110376695>. PMID: 20823080 **Ineligible study design**
13. Amann B, Grunze H, Vieta E, et al. Antiepileptic drugs and mood stability. *Clinical EEG & Neuroscience: Official Journal of the EEG & Clinical Neuroscience Society (ENCS)*. 2007 Apr;38(2):116-23. PMID: 17515177 **Ineligible study design**
14. Amrollahi Z, Rezaei F, Salehi B, et al. Double-blind, randomized, placebo-controlled 6-week study on the efficacy and safety of the tamoxifen adjunctive to lithium in acute bipolar mania. *Journal of Affective Disorders*. 2011 Mar;129(1-3):327-31. doi: <http://dx.doi.org/10.1016/j.jad.2010.08.015>. PMID: 20843556 **Bipolar not analyzed separately**
15. Amsterdam JD, Brunswick DJ. Antidepressant monotherapy for bipolar type II major depression. *Bipolar Disorders*. 2003 Dec;5(6):388-95. PMID: 14636362 **Ineligible study design**
16. Amsterdam JD, Garcia-Espana F, Fawcett J, et al. Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *Journal of Clinical Psychopharmacology*. 1998 Dec;18(6):435-40. PMID: 9864074 **Over 50% dropout rate**
17. Amsterdam JD, Lorenzo-Luaces L, DeRubeis RJ. Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression. *Bipolar Disorders*. 2016 01 Nov;18(7):563-70. doi: <http://dx.doi.org/10.1111/bdi.12442>. PMID: 613301128 **Duplicate reference**
18. Amsterdam JD, Luo L, Shults J. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. *The British Journal of Psychiatry*. 2013 2013;202(4):301-6. doi: <http://dx.doi.org/10.1192/bjp.bp.111.104711>. PMID: 23099447 **Over 50% dropout rate**
19. Amsterdam JD, Shults J. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. *International Clinical Psychopharmacology*. 2005 Sep;20(5):257-64. PMID: 16096516 **Fewer than 11 subjects per arm**
20. Anand A, Gunn AD, Barkay G, et al. Early antidepressant effect of memantine during augmentation of lamotrigine inadequate response in bipolar depression: a double-blind, randomized, placebo-controlled trial. *Bipolar Disorders*. 2012 Feb;14(1):64-70. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00971.x>. PMID: 22329473 **No eligible outcomes reported**
21. Anfang MK, Pope HG, Jr. Treatment of neuroleptic-induced akathisia with nicotine patches. *Psychopharmacology*. 1997 1997;134(2):153-6. doi: <http://dx.doi.org/10.1007/s002130050436>. **No eligible outcomes reported**
22. Anonymous. Treatment of special populations with the atypical antipsychotics. Collaborative Working Group on Clinical Trial Evaluations. *Journal of Clinical Psychiatry*. 1998;59 Suppl 12:46-52. PMID: 9766620 **Ineligible study design**
23. Anonymous. Emerging therapies for bipolar depression. *Journal of Clinical Psychiatry*. 2006 Jul;67(7):1140-51. PMID: 17107231 **Ineligible study design**

24. Anonymous. Asenapine: a less effective, yet, more dangerous neuroleptic! Prescrire International. 2012 Oct;21(131):229-32. PMID: 23185842 **Ineligible study design**
25. Anonymous. Correction: Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: Randomised controlled pilot trial (The British Journal of Psychiatry 206 (58-66)). British Journal of Psychiatry. 2015 01 Feb;206(2):169. doi: <http://dx.doi.org/10.1192/bjp.206.2.169>. PMID: 602333099
Duplicate reference
26. Arbaizar B, Dierssen-Sotos T, Gomez-Acebo I, et al. Aripiprazole in major depression and mania: meta-analyses of randomized placebo-controlled trials. General Hospital Psychiatry. 2009 Sep-Oct;31(5):478-83. doi: <http://dx.doi.org/10.1016/j.genhosppsych.2009.05.005>. PMID: 19703642 **Ineligible study design**
27. Azorin JM, Kaladjian A. An update on the treatment of bipolar depression. Expert Opinion on Pharmacotherapy. 2009 Feb;10(2):161-72. doi: <http://dx.doi.org/10.1517/14656560802653172>. PMID: 19236191 **Ineligible study design**
28. Azorin JM, Sapin C, Weiller E. Effect of asenapine on manic and depressive symptoms in bipolar I patients with mixed episodes: results from post hoc analyses. Journal of Affective Disorders. 2013 Feb 15;145(1):62-9. doi: <http://dx.doi.org/10.1016/j.jad.2012.07.013>. PMID: 22868059 **Ineligible study design**
29. Azorin J-M, Bowden CL, Garay RP, et al. Possible new ways in the pharmacological treatment of bipolar disorder and comorbid alcoholism. Neuropsychiatric Disease and Treatment. 2010 3, 2010;6(1):37-46.
Ineligible study design
30. Baek JH, Bernstein EE, Nierenberg AA. One-carbon metabolism and bipolar disorder. Australian and New Zealand Journal of Psychiatry. 2013 2013;47(11):1013-8. doi: <http://dx.doi.org/10.1177/0004867413502091>. **Ineligible study design**
31. Baethge C. A bold meta-analysis on suicidality in bipolar disorder. Bipolar Disorders. 2015 Feb;17(1):17-8. doi: <http://dx.doi.org/10.1111/bdi.12263>. PMID: 25346160 **Ineligible study design**
32. Baethge C, Baldessarini RJ, Mathiske-Schmidt K, et al. Long-term combination therapy versus monotherapy with lithium and carbamazepine in 46 bipolar I patients. Journal of Clinical Psychiatry. 2005 Feb;66(2):174-82. PMID: 15705002 **No eligible outcomes reported**
33. Baethge C, Smolka MN, Gruschka P, et al. Does prophylaxis-delay in bipolar disorder influence outcome? Results from a long-term study of 147 patients. Acta Psychiatrica Scandinavica. 2003 Apr;107(4):260-7. PMID: 12662248 **Ineligible study design**
34. Bailine S, Fink M, Knapp R, et al. Electroconvulsive therapy is equally effective in unipolar and bipolar depression. Acta Psychiatrica Scandinavica. 2010 Jun;121(6):431-6. doi: <http://dx.doi.org/10.1111/j.1600-0447.2009.01493.x>. PMID: 19895623 **No eligible outcomes reported**
35. Bailine SH, Rifkin A, Kayne E, et al. Comparison of bifrontal and bitemporal ECT for major depression. American Journal of Psychiatry. 2000 Jan;157(1):121-3. PMID: 10618025 **Bipolar not analyzed separately**

36. Baker RW, Goldberg JF, Tohen M, et al. The impact of response to previous mood stabilizer therapy on response to olanzapine versus placebo for acute mania. *Bipolar Disorders*. 2002 Feb;4(1):43-9. PMID: 12047494 **Ineligible study design**
37. Baker RW, Milton DR, Stauffer VL, et al. Placebo-controlled trials do not find association of olanzapine with exacerbation of bipolar mania. *Journal of Affective Disorders*. 2003 Jan;73(1-2):147-53. PMID: 12507747 **Over 50% dropout rate**
38. Baker RW, Tohen M, Fawcett J, et al. Acute dysphoric mania: treatment response to olanzapine versus placebo. *Journal of Clinical Psychopharmacology*. 2003 Apr;23(2):132-7. PMID: 12640214 **Over 50% dropout rate**
39. Baldassano C. Pharmacologic treatment of bipolar disorder. *Cns Spectrums*. 2010 Feb;15(2 Suppl 3):10-3; discussion 7. PMID: 20414160 **Ineligible study design**
40. Baldassano CF, Ballas CA, O'Reardon JP. Rethinking the treatment paradigm for bipolar depression: the importance of long-term management. *Cns Spectrums*. 2004 Sep;9(9 Suppl 9):11-8. PMID: 15361807 **Ineligible study design**
41. Baldessarini RJ, Faedda GL, Offidani E, et al. Antidepressant-associated mood-switching and transition from unipolar major depression to bipolar disorder: a review. *Journal of Affective Disorders*. 2013 May 15;148(1):129-35. doi: <http://dx.doi.org/10.1016/j.jad.2012.10.033>. PMID: 23219059 **Ineligible study design**
42. Baldessarini RJ, Hennen J, Wilson M, et al. Olanzapine versus placebo in acute mania: treatment responses in subgroups. *Journal of Clinical Psychopharmacology*. 2003 Aug;23(4):370-6. PMID: 12920413 **Over 50% dropout rate**
43. Baldessarini RJ, Pompili M, Tondo L, et al. Antidepressants and Suicidal Behavior: Are We Hurting Or Helping? [References]. *Clinical Neuropsychiatry: Journal of Treatment Evaluation*. 2005 2005;2(1):73-5. **Ineligible study design**
44. Baldessarini RJ, Tondo L. Does lithium treatment still work? Evidence of stable responses over three decades. *Archives of General Psychiatry*. 2000 Feb;57(2):187-90. PMID: 10665622 **Ineligible study design**
45. Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review.[Erratum appears in *Bipolar Disord*. 2007 May;9(3):314]. *Bipolar Disorders*. 2006 Oct;8(5 Pt 2):625-39. PMID: 17042835 **Ineligible study design**
46. Ballard ED, Vande Voort JL, Luckenbaugh DA, et al. Acute risk factors for suicide attempts and death: prospective findings from the STEP-BD study. *Bipolar Disorders*. 2016 01 Jun;18(4):363-72. doi: <http://dx.doi.org/10.1111/bdi.12397>. PMID: 611080830 **Not treating bipolar**
47. Ban TA. Fifty years chlorpromazine: a historical perspective. *Neuropsychiatric disease and treatment*. 2007;3(4):495-500. PMID: 19300578 **Ineligible study design**
48. Baptista T, Rangel N, Fernandez V, et al. Metformin as an adjunctive treatment to control body weight and metabolic dysfunction during olanzapine administration: a multicentric, double-blind, placebo-controlled

- trial. Schizophrenia Research. 2007 Jul;93(1-3):99-108. PMID: 17490862 **Bipolar not analyzed separately**
49. Barak Y, Kimhi R, Weizman R. Is selectivity for serotonin uptake associated with a reduced emergence of manic episodes in depressed patients? International Clinical Psychopharmacology. 2000 Jan;15(1):53-6. PMID: 10836288 **Not bipolar disorder**
 50. Barbini B, Colombo C, Benedetti F, et al. The unipolar-bipolar dichotomy and the response to sleep deprivation. Psychiatry Research. 1998 Jun 2;79(1):43-50. PMID: 9676825 **Ineligible study design**
 51. Berekatani M, Jahangard L, Haghighi M, et al. Bifrontal versus bitemporal electroconvulsive therapy in severe manic patients. Journal of ECT. 2008 Sep;24(3):199-202. doi: <http://dx.doi.org/10.1097/YCT.0b013e3181624b5d>. PMID: 18772704 **No eligible outcomes reported**
 52. Basu R, Brar JS, Chengappa KNR, et al. The prevalence of the metabolic syndrome in patients with schizoaffective disorder - bipolar subtype. Bipolar Disorders. 2004 2004;6(4):314-8. doi: <http://dx.doi.org/10.1111/j.1399-5618.2004.00126.x>. **Ineligible study design**
 53. Battaglia J, Lindborg SR, Alaka K, et al. Calming versus sedative effects of intramuscular olanzapine in agitated patients. American Journal of Emergency Medicine. 2003 May;21(3):192-8. PMID: 12811711 **Ineligible study design**
 54. Bauer IE, Galvez JF, Hamilton JE, et al. Lifestyle interventions targeting dietary habits and exercise in bipolar disorder: A systematic review. Journal of Psychiatric Research. 2016 01 Mar;74:1-7. doi: <http://dx.doi.org/10.1016/j.jpsychires.2015.12.006>. PMID: 608386673 **Ineligible study design**
 55. Bauer M, Rasgon N, Grof P, et al. Do antidepressants influence mood patterns? A naturalistic study in bipolar disorder. European Psychiatry: the Journal of the Association of European Psychiatrists. 2006 Jun;21(4):262-9. PMID: 16782312 **No eligible outcomes reported**
 56. Bauer M, Ritter P, Grunze H, et al. Treatment options for acute depression in bipolar disorder. Bipolar Disorders. 2012 May;14 Suppl 2:37-50. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.00991.x>. PMID: 22510035 **Ineligible study design**
 57. Bauer MS. An evidence-based review of psychosocial treatments for bipolar disorder. Psychopharmacology Bulletin. 2001;35(3):109-34. PMID: 12397882 **Ineligible study design**
 58. Bauer MS, Mitchner L. What is a "mood stabilizer"? An evidence-based response. American Journal of Psychiatry. 2004 Jan;161(1):3-18. PMID: 14702242 **Ineligible study design**
 59. Bauer MS, Wisniewski SR, Marangell LB, et al. Are antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Journal of Clinical Psychiatry. 2006 Jan;67(1):48-55. PMID: 16426088 **No eligible outcomes reported**
 60. Bech P, Vendsborg PB, Rafaelsen OJ. Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine. Acta Psychiatr Scand. 1976 Jan;53(1):70-81. PMID: 1251757 **No eligible outcomes reported**

61. Belete H. Use of physical restraints among patients with bipolar disorder in Ethiopian Mental Specialized Hospital, outpatient department: cross-sectional study. *International Journal of Bipolar Disorders*. 2017 01 Dec;5 (1) (no pagination)(17)doi: <http://dx.doi.org/10.1186/s40345-017-0084-6>. PMID: 614975526
Ineligible intervention
62. Bellantuono C, Barraco A, Rossi A, et al. The management of bipolar mania: a national survey of baseline data from the EMBLEM study in Italy. *BMC Psychiatry*. 2007;7:33. PMID: 17640381 **Ineligible study design**
63. Bellivier F, Belzeaux R, Scott J, et al. Anticonvulsants and suicide attempts in bipolar I disorders. *Acta Psychiatrica Scandinavica*. 2017 01 May;135(5):470-8. doi: <http://dx.doi.org/10.1111/acps.12709>. PMID: 614392589 **Not treating bipolar**
64. Belmaker RH. Patient history must be incorporated into any guidelines. *Bipolar Disorders*. 2009 2009;11(7):772. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00743.x>. **Ineligible study design**
65. Benedetti F, Barbini B, Campori E, et al. Dopamine agonist amineptine prevents the antidepressant effect of sleep deprivation. *Psychiatry Research*. 1996 Dec 20;65(3):179-84. PMID: 9029666 **Ineligible study design**
66. Benedetti F, Barbini B, Campori E, et al. Sleep phase advance and lithium to sustain the antidepressant effect of total sleep deprivation in bipolar depression: new findings supporting the internal coincidence model? *Journal of Psychiatric Research*. 2001 Nov-Dec;35(6):323-9. PMID: 11684139 **Ineligible study design**
67. Benedetti F, Campori E, Barbini B, et al. Dopaminergic augmentation of sleep deprivation effects in bipolar depression. *Psychiatry Research*. 2001 Nov 30;104(3):239-46. PMID: 11728613 **Ineligible study design**
68. Benedetti F, Colombo C, Pontiggia A, et al. Morning light treatment hastens the antidepressant effect of citalopram: A placebo-controlled trial. *Journal of Clinical Psychiatry*. 2003 2003;64(6):648-53. doi: <http://dx.doi.org/10.4088/JCP.v64n0605>. **No eligible outcomes reported**
69. Berk M. Lamotrigine and the treatment of mania in bipolar disorder. *European Neuropsychopharmacology*. 1999 Aug;9 Suppl 4:S119-23. PMID: 10524838 **Duplicate reference**
70. Berk M, Copolov DL, Dean O, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. *Biological Psychiatry*. 2008 Sep 15;64(6):468-75. doi: <http://dx.doi.org/10.1016/j.biopsych.2008.04.022>. PMID: 18534556 **Ineligible intervention**
71. Berk M, Ng F, Wang WV, et al. Going up in smoke: tobacco smoking is associated with worse treatment outcomes in mania. *Journal of Affective Disorders*. 2008 Sep;110(1-2):126-34. doi: <http://dx.doi.org/10.1016/j.jad.2008.01.018>. PMID: 18280579 **No eligible outcomes reported**
72. Berk M, Tiller JW, Zhao J, et al. Effects of asenapine in bipolar I patients meeting proxy criteria for moderate-to-severe mixed major depressive episodes: A post hoc analysis. *Journal of Clinical Psychiatry*. 2015 01 Jun 2015;76(6):728-34. doi: <http://dx.doi.org/10.4088/JCP.13m08827>. PMID: 605004625 **No eligible outcomes reported**

73. Bernardo M, Dodd S, Gama CS, et al. Effects of N-acetylcysteine on substance use in bipolar disorder: A randomised placebo-controlled clinical trial. *Acta Neuropsychiatrica*. 2009 2009;21(6):285-91. doi: <http://dx.doi.org/10.1111/j.1601-5215.2009.00397.x>. **No eligible outcomes reported**
74. Bersani FS, Minichino A, Bernabei L, et al. Prefronto-cerebellar tDCS enhances neurocognition in euthymic bipolar patients. Findings from a placebo-controlled neuropsychological and psychophysiological investigation. *Journal of Affective Disorders*. 2017 01 Feb;209:262-9. doi: <http://dx.doi.org/10.1016/j.jad.2016.11.037>. PMID: 613575159 **Ineligible study design**
75. Bersudsky Y. Phenytoin: an anti-bipolar anticonvulsant? *International Journal of Neuropsychopharmacology*. 2006 Aug;9(4):479-84. PMID: 16202184 **Duplicate reference**
76. Bersudsky Y, Applebaum J, Gaiduk Y, et al. Valnoctamide as a valproate substitute with low teratogenic potential in mania: a double-blind, controlled, add-on clinical trial. *Bipolar Disorders*. 2010 Jun;12(4):376-82. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00828.x>. PMID: 20636634 **Bipolar not analyzed separately**
77. Beynon S, Soares-Weiser K, Woolacott N, et al. Psychosocial interventions for the prevention of relapse in bipolar disorder: systematic review of controlled trials. *British Journal of Psychiatry*. 2008 Jan;192(1):5-11. doi: <http://dx.doi.org/10.1192/bjp.bp.107.037887>. PMID: 18174500 **Ineligible study design**
78. Beynon S, Soares-Weiser K, Woolacott N, et al. Pharmacological interventions for the prevention of relapse in bipolar disorder: a systematic review of controlled trials. *Journal of Psychopharmacology*. 2009 Jul;23(5):574-91. doi: <http://dx.doi.org/10.1177/0269881108093885>. PMID: 18635701 **Ineligible study design**
79. Bhana N, Perry CM. Olanzapine: a review of its use in the treatment of bipolar I disorder. *CNS Drugs*. 2001;15(11):871-904. PMID: 11700151 **Ineligible study design**
80. Bhugra D, Ayonrinde O, Butler G, et al. A randomised controlled trial of assertive outreach vs. treatment as usual for black people with severe mental illness. *Epidemiology & Psychiatric Science*. 2011 Mar;20(1):83-9. PMID: 21657119 **Bipolar not analyzed separately**
81. Biel MG, Peselow E, Mulcare L, et al. Continuation versus discontinuation of lithium in recurrent bipolar illness: a naturalistic study. *Bipolar Disorders*. 2007 Aug;9(5):435-42. PMID: 17680913 **No eligible outcomes reported**
82. Bjorgvinsson T, Kertz SJ, Bigda-Peyton JS, et al. Effectiveness of cognitive behavior therapy for severe mood disorders in an acute psychiatric naturalistic setting: A benchmarking study. *Cognitive Behaviour Therapy*. 2014 2014;43(3):209-20. doi: <http://dx.doi.org/10.1080/16506073.2014.901988>. **Bipolar not analyzed separately**
83. Bobo WV, Reilly-Harrington NA, Ketter TA, et al. Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: results from the Bipolar CHOICE trial. *Journal of Affective Disorders*. 2014 Jun;161:30-5. doi: <http://dx.doi.org/10.1016/j.jad.2014.02.046>. PMID: 24751304 **Ineligible study design**
84. Bobo WV, Reilly-Harrington NA, Ketter TA, et al. Complexity of illness and adjunctive benzodiazepine use in outpatients with bipolar I or II disorder: results from the Bipolar CHOICE study. *Journal of Clinical*

- Psychopharmacology. 2015 Feb;35(1):68-74. doi: <http://dx.doi.org/10.1097/JCP.0000000000000257>. PMID: 25514063 **No eligible outcomes reported**
85. Bogart GT, Chavez B. Safety and efficacy of quetiapine in bipolar depression. *Annals of Pharmacotherapy*. 2009 Nov;43(11):1848-56. doi: <http://dx.doi.org/10.1345/aph.1M193>. PMID: 19809011 **Ineligible study design**
 86. Boland EM, Stange JP, Molz Adams A, et al. Associations between sleep disturbance, cognitive functioning and work disability in Bipolar Disorder. *Psychiatry Research*. 2015 Dec 15;230(2):567-74. doi: <http://dx.doi.org/10.1016/j.psychres.2015.09.051>. PMID: 26474660 **Not treating bipolar**
 87. Bonafede M, Locklear JC, Wahlqvist P, et al. Impact of once-daily extended-release quetiapine fumarate on hospitalization length in patients with acute bipolar mania. *Journal of Comparative Effectiveness Research*. 2015 Jan;4(1):51-9. doi: <http://dx.doi.org/10.2217/ce.14.48>. PMID: 25168473 **No eligible outcomes reported**
 88. Bond DJ, Lam RW, Yatham LN. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. *Journal of Affective Disorders*. 2010 Aug;124(3):228-34. doi: <http://dx.doi.org/10.1016/j.jad.2009.11.008>. PMID: 20044142 **Ineligible study design**
 89. Bond DJ, Pratoomsri W, Yatham LN. Depot antipsychotic medications in bipolar disorder: a review of the literature. *Acta Psychiatrica Scandinavica, Supplementum*. 2007(434):3-16. PMID: 17688458 **Ineligible study design**
 90. Bonnin CM, Torrent C, Arango C, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *British Journal of Psychiatry*. 2016 January;208(1):87-93. doi: <http://dx.doi.org/10.1192/bjp.bp.114.162123>. PMID: 608072552 **Duplicate reference**
 91. Bonnin CM, Torrent C, Arango C, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *British Journal of Psychiatry*. 2016 Jan;208(1):87-93. doi: <http://dx.doi.org/10.1192/bjp.bp.114.162123>. PMID: 26541692 **Ineligible study design**
 92. Bos EH, Merea R, van den Brink E, et al. Mindfulness training in a heterogeneous psychiatric sample: outcome evaluation and comparison of different diagnostic groups. *Journal of Clinical Psychology*. 2014 Jan;70(1):60-71. doi: <http://dx.doi.org/10.1002/jclp.22008>. PMID: 23801545 **Ineligible study design**
 93. Bottlender R, Rudolf D, Strauss A, et al. Mood-stabilisers reduce the risk of developing antidepressant-induced manic states in acute treatment of bipolar I depressed patients. *Journal of Affective Disorders*. 2001 Mar;63(1-3):79-83. PMID: 11246083 **No eligible outcomes reported**
 94. Bourin M, Lambert O, Guitton B. Treatment of acute mania--from clinical trials to recommendations for clinical practice. *Human Psychopharmacology*. 2005 Jan;20(1):15-26. PMID: 15568205 **Ineligible study design**
 95. Bowden C, Boyer P. Treatment pathways for bipolar disorder in the USA and Europe: convergence or divergence? *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2003 Dec;18 Suppl 1:19s-24s. PMID: 23573637 **Ineligible study design**

96. Bowden C, Maier W. Bipolar disorder and personality disorder. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2003 Dec;18 Suppl 1:9s-12s. PMID: 23573635 **Ineligible study design**
97. Bowden CL. Dosing strategies and time course of response to antimanic drugs. *Journal of Clinical Psychiatry*. 1996;57 Suppl 13:4-9; discussion 10-2. PMID: 8970500 **Ineligible study design**
98. Bowden CL. Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. *Journal of Clinical Psychiatry*. 1998;59 Suppl 6:13-9; discussion 20. PMID: 9674932 **Ineligible study design**
99. Bowden CL. Efficacy of lithium in mania and maintenance therapy of bipolar disorder. *Journal of Clinical Psychiatry*. 2000;61 Suppl 9:35-40. PMID: 10826659 **Ineligible study design**
100. Bowden CL. The ability of lithium and other mood stabilizers to decrease suicide risk and prevent relapse. *Current Psychiatry Reports*. 2000 Dec;2(6):490-4. PMID: 11123000 **Ineligible study design**
101. Bowden CL. Novel treatments for bipolar disorder. *Expert Opinion on Investigational Drugs*. 2001 Apr;10(4):661-71. PMID: 11281816 **Ineligible study design**
102. Bowden CL. Acute and maintenance treatment with mood stabilizers. *International Journal of Neuropsychopharmacology*. 2003 Sep;6(3):269-75. PMID: 12974993 **Ineligible study design**
103. Bowden CL. Valproate. *Bipolar Disorders*. 2003 Jun;5(3):189-202. PMID: 12780873 **Ineligible study design**
104. Bowden CL. Treatment options for bipolar depression. *Journal of Clinical Psychiatry*. 2005;66 Suppl 1:3-6. PMID: 15693745 **Ineligible study design**
105. Bowden CL. Anticonvulsants in bipolar disorders: current research and practice and future directions. *Bipolar Disorders*. 2009 Jun;11 Suppl 2:20-33. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00708.x>. PMID: 19538683 **Ineligible study design**
106. Bowden CL. Pharmacological treatments for bipolar disorder: Present recommendations and future prospects. Manji, Husseini K [Ed]. 2011 **Ineligible study design**
107. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. The Depakote Mania Study Group.[Erratum appears in JAMA 1994 Jun 15;271(23):1830]. *JAMA*. 1994 Mar 23-30;271(12):918-24. PMID: 8120960 **Over 50% dropout rate**
108. Bowden CL, Calabrese JR, Ketter TA, et al. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar I disorder. *American Journal of Psychiatry*. 2006 Jul;163(7):1199-201. PMID: 16816224 **Over 50% dropout rate**
109. Bowden CL, Janicak PG, Orsulak P, et al. Relation of serum valproate concentration to response in mania. *American Journal of Psychiatry*. 1996 Jun;153(6):765-70. PMID: 8633687 **Ineligible study design**
110. Bowden CL, Ketter TA, Sachs GS, et al. Focus on bipolar disorder treatment. *Journal of Clinical Psychiatry*. 2005 Dec;66(12):1598-609. PMID: 16401164 **Ineligible study design**

111. Bowden CL, Mintz J, Tohen M. Multi-state outcome analysis of treatments (MOAT): application of a new approach to evaluate outcomes in longitudinal studies of bipolar disorder. *Molecular Psychiatry*. 2016 Feb;21(2):237-42. doi: <http://dx.doi.org/10.1038/mp.2015.21>. PMID: 25778474 **Duplicate reference**
112. Bowden CL, Singh V. Valproate in bipolar disorder: 2000 onwards. *Acta Psychiatrica Scandinavica, Supplementum*. 2005(426):13-20. PMID: 15833096 **Ineligible study design**
113. Bowden CL, Singh V. Lamotrigine (Lamictal IR) for the treatment of bipolar disorder. *Expert Opinion on Pharmacotherapy*. 2012 Dec;13(17):2565-71. doi: <http://dx.doi.org/10.1517/14656566.2012.741590>. PMID: 23140205 **Ineligible study design**
114. Bowden CL, Singh V, Weisler R, et al. Lamotrigine vs. lamotrigine plus divalproex in randomized, placebo-controlled maintenance treatment for bipolar depression. *Acta Psychiatrica Scandinavica*. 2012 Nov;126(5):342-50. doi: <http://dx.doi.org/10.1111/j.1600-0447.2012.01890.x>. PMID: 22708645 **Over 50% dropout rate**
115. Bradford DW, Cunningham NT, Slubicki MN, et al. An evidence synthesis of care models to improve general medical outcomes for individuals with serious mental illness: a systematic review. *Journal of Clinical Psychiatry*. 2013 Aug;74(8):e754-64. doi: <http://dx.doi.org/10.4088/JCP.12r07666>. PMID: 24021516 **Ineligible study design**
116. Brambilla P, Barale F, Soares JC. Perspectives on the use of anticonvulsants in the treatment of bipolar disorder. *International Journal of Neuropsychopharmacology*. 2001 Dec;4(4):421-46. PMID: 11806868 **Ineligible study design**
117. Brambilla P, Barale F, Soares JC. Atypical antipsychotics and mood stabilization in bipolar disorder. *Psychopharmacology*. 2003 Apr;166(4):315-32. PMID: 12607072 **Ineligible study design**
118. Bridle C, Palmer S, Bagnall AM, et al. A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder. *Health Technology Assessment (Winchester, England)*. 2004 May;8(19):iii-iv, 1-187. PMID: 15147609 **Ineligible study design**
119. Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs. lamotrigine in the 6-month treatment of bipolar I depression. *International Journal of Neuropsychopharmacology*. 2009 Jul;12(6):773-82. doi: <http://dx.doi.org/10.1017/S1461145708009735>. PMID: 19079815 **Over 50% dropout rate**
120. Brown ES. Management of comorbid bipolar disorder and substance abuse. *Journal of Clinical Psychiatry*. 2006 Aug;67(8):e05. PMID: 17107268 **Ineligible study design**
121. Brown ES, Gabrielson B. A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. *Journal of Affective Disorders*. 2012 Dec 20;143(1-3):257-60. doi: <http://dx.doi.org/10.1016/j.jad.2012.05.006>. PMID: 22974472 **Not treating bipolar**
122. Brown ES, Garza M, Carmody TJ. A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *Journal of Clinical Psychiatry*. 2008 May;69(5):701-5. PMID: 18312058 **No eligible outcomes reported**

123. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. *Journal of Clinical Psychopharmacology*. 2007 Oct;27(5):498-502. PMID: 17873684 **Not treating bipolar**
124. Brown ES, Nejtek VA, Perantie DC, et al. Quetiapine in bipolar disorder and cocaine dependence. *Bipolar Disorders*. 2002 Dec;4(6):406-11. PMID: 12519101 **Fewer than 11 subjects per arm**
125. Brown ES, Todd JP, Hu LT, et al. A randomized, double-blind, placebo-controlled trial of citicoline for cocaine dependence in bipolar i disorder. *American Journal of Psychiatry*. 2015 01 Oct;172(10):1014-21. doi: <http://dx.doi.org/10.1176/appi.ajp.2015.14070857>. PMID: 2015417503 **Ineligible study design**
126. Buchheit J, Uhring J, Sergeant P, et al. Can preoperative CRP levels predict infections of bipolar hemiarthroplasty performed for femoral neck fracture? A retrospective, multicenter study. *European journal of orthopaedic surgery & traumatologie*. 2015 Jan;25(1):117-21. doi: <http://dx.doi.org/10.1007/s00590-014-1449-5>. PMID: 24719083 **Not bipolar disorder**
127. Buckley PF. Update on the treatment and management of schizophrenia and bipolar disorder. *Cns Spectrums*. 2008 Feb;13(2 Suppl 1):1-10; quiz 1-2. PMID: 18227747 **Ineligible study design**
128. Buckley PF, Paulsson B, Brecher M. Treatment of agitation and aggression in bipolar mania: efficacy of quetiapine. *Journal of Affective Disorders*. 2007;100 Suppl 1:S33-43. PMID: 17376537 **No eligible outcomes reported**
129. Burdick KE, Braga RJ, Gopin CB, et al. Dopaminergic influences on emotional decision making in euthymic bipolar patients. *Neuropsychopharmacology*. 2014 Jan;39(2):274-82. doi: <http://dx.doi.org/10.1038/npp.2013.177>. PMID: 23884342 **No eligible outcomes reported**
130. Burgess S, Geddes J, Hawton K, et al. Lithium for maintenance treatment of mood disorders. *Cochrane Database of Systematic Reviews*. 2001(3):CD003013. PMID: 11687035 **Ineligible study design**
131. Busby KK, Sajatovic M. Patient, treatment, and systems-level factors in bipolar disorder nonadherence: A summary of the literature. *CNS Neuroscience & Therapeutics*. 2010 2010;16(5):308-15. doi: <http://dx.doi.org/10.1111/j.1755-5949.2010.00191.x>. **Ineligible study design**
132. Busch AB, He Y, Zelevinsky K, et al. Predicting Participation in Psychiatric Randomized Controlled Trials: Insights From the STEP-BD. *Psychiatric Services*. 2015 Aug 1;66(8):817-23. doi: <http://dx.doi.org/10.1176/appi.ps.201300557>. PMID: 25828873 **Not treating bipolar**
133. Bushe C, Shaw M. Prevalence of hyperprolactinaemia in a naturalistic cohort of schizophrenia and bipolar outpatients during treatment with typical and atypical antipsychotics. *Journal of Psychopharmacology*. 2007 Sep;21(7):768-73. PMID: 17606473 **Ineligible study design**
134. Calabrese J, Rajagopalan K, Ng-Mak D, et al. Effect of lurasidone on meaningful change in health-related quality of life in patients with bipolar depression. *International Clinical Psychopharmacology*. 2016 13 Apr;31(3):147-54. doi: <http://dx.doi.org/10.1097/YIC.0000000000000116>. PMID: 607489863 **No eligible outcomes reported**
135. Calabrese JR, Goldberg JF, Ketter TA, et al. Recurrence in bipolar I disorder: a post hoc analysis excluding relapses in two double-blind maintenance studies. *Biological Psychiatry*. 2006 Jun 1;59(11):1061-4. PMID: 16769295 **Ineligible study design**

136. Calabrese JR, Rapport DJ, Shelton MD, et al. Clinical studies on the use of lamotrigine in bipolar disorder. *Neuropsychobiology*. 1998 Oct;38(3):185-91. PMID: 9778607 **Ineligible study design**
137. Calabrese JR, Rapport DJ, Youngstrom EA, et al. New data on the use of lithium, divalproate, and lamotrigine in rapid cycling bipolar disorder. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2005 Mar;20(2):92-5. PMID: 15797691 **Duplicate reference**
138. Calabrese JR, Shelton MD, Rapport DJ, et al. Long-term treatment of bipolar disorder with lamotrigine. *Journal of Clinical Psychiatry*. 2002;63 Suppl 10:18-22. PMID: 12392349 **Ineligible study design**
139. Calabrese JR, Sullivan JR, Bowden CL, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *Journal of Clinical Psychiatry*. 2002 Nov;63(11):1012-9. PMID: 12444815 **Bipolar not analyzed separately**
140. Calabrese JR, Vieta E, Shelton MD. Latest maintenance data on lamotrigine in bipolar disorder. *European Neuropsychopharmacology*. 2003 Aug;13 Suppl 2:S57-66. PMID: 12957721 **Ineligible study design**
141. Camm AJ, Karayal ON, Meltzer H, et al. Ziprasidone and the corrected QT interval: a comprehensive summary of clinical data. *CNS Drugs*. 2012 Apr 1;26(4):351-65. doi: <http://dx.doi.org/10.2165/11599010-000000000-00000>. PMID: 22452529 **Ineligible study design**
142. Cardoso Tde A, Campos Mondin T, Reyes AN, et al. Biological Rhythm and Bipolar Disorder: Twelve-Month Follow-Up of a Randomized Clinical Trial. *Journal of Nervous & Mental Disease*. 2015 Oct;203(10):792-7. doi: <http://dx.doi.org/10.1097/NMD.0000000000000369>. PMID: 26348588 **Over 50% dropout rate**
143. Carey TS, Williams JW, Jr., Oldham JM, et al. Gabapentin in the treatment of mental illness: the echo chamber of the case series. *Journal of Psychiatric Practice*. 2008 Mar;14 Suppl 1:15-27. doi: <http://dx.doi.org/10.1097/01.pra.0000333584.75741.45>. PMID: 19034206 **Ineligible study design**
144. Carney SM, Goodwin GM. Lithium - a continuing story in the treatment of bipolar disorder. *Acta Psychiatrica Scandinavica, Supplementum*. 2005(426):7-12. PMID: 15833095 **Ineligible study design**
145. Carta MG, Hardoy MC, Hardoy MJ, et al. The clinical use of gabapentin in bipolar spectrum disorders. *Journal of Affective Disorders*. 2003 Jun;75(1):83-91. PMID: 12781355 **Ineligible study design**
146. Cassano GB, Heinze G, Loo H, et al. A double-blind comparison of tianeptine, imipramine and placebo in the treatment of major depressive episodes. *European Psychiatry*. 1996;11(5):254-9. doi: [http://dx.doi.org/10.1016/0924-9338\(96\)2982332-7](http://dx.doi.org/10.1016/0924-9338(96)2982332-7). **Bipolar not analyzed separately**
147. Castle DJ. Bipolar mixed states: still mixed up? *Current Opinion in Psychiatry*. 2014 Jan;27(1):38-42. doi: <http://dx.doi.org/10.1097/YCO.0000000000000029>. PMID: 24270474 **Ineligible study design**
148. Cavazzoni PA, Berg PH, Kryzhanovskaya LA, et al. Comparison of treatment-emergent extrapyramidal symptoms in patients with bipolar mania or schizophrenia during olanzapine clinical trials. *Journal of Clinical Psychiatry*. 2006 Jan;67(1):107-13. PMID: 16426096 **Ineligible study design**

149. Cazorla P, Zhao J, Mackle M, et al. Asenapine effects on individual Young Mania Rating Scale items in bipolar disorder patients with acute manic or mixed episodes: A pooled analysis. *Neuropsychiatric Disease and Treatment*. 2013 28, 2013;9:409-13. **No eligible outcomes reported**
150. Ceron-Litvoc D, Soares BG, Geddes J, et al. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Human Psychopharmacology*. 2009 Jan;24(1):19-28. doi: <http://dx.doi.org/10.1002/hup.990>. PMID: 19053079 **Ineligible study design**
151. Cerullo MA, Strakowski SM. A systematic review of the evidence for the treatment of acute depression in bipolar I disorder. *Cns Spectrums*. 2013 Aug;18(4):199-208. doi: <http://dx.doi.org/10.1017/S1092852913000102>. PMID: 23507138 **Ineligible study design**
152. Chafetz L, White M, Collins-Bride G, et al. Clinical trial of wellness training: health promotion for severely mentally ill adults. *Journal of Nervous & Mental Disease*. 2008 Jun;196(6):475-83. doi: <http://dx.doi.org/10.1097/NMD.0b013e31817738de>. PMID: 18552625 **Bipolar not analyzed separately**
153. Chan HY, Jou SH, Juang YY, et al. A single-blind, comparative study of zotepine versus haloperidol in combination with a mood stabilizer for patients with moderate-to-severe mania. *Psychiatry & Clinical Neurosciences*. 2010 Apr;64(2):162-9. doi: <http://dx.doi.org/10.1111/j.1440-1819.2010.02066.x>. PMID: 20447012 **Fewer than 11 subjects per arm**
154. Chandler D, Meisel J, Hu TW, et al. Client outcomes in a three-year controlled study of an integrated service agency model. *Psychiatric Services*. 1996 Dec;47(12):1337-43. PMID: 9117472 **Bipolar not analyzed separately**
155. Chandramouli J. Newer anticonvulsant drugs in neuropathic pain and bipolar disorder. *Journal of Pain & Palliative Care Pharmacotherapy*. 2002;16(4):19-37. PMID: 14635823 **Ineligible study design**
156. Chapel S, Chiu YY, Hsu J, et al. Lurasidone Dose Response in Bipolar Depression: A Population Dose-response Analysis. *Clinical Therapeutics*. 2016 Jan 1;38(1):4-15. doi: <http://dx.doi.org/10.1016/j.clinthera.2015.11.013>. PMID: 26730454 **Ineligible study design**
157. Chen D-G. Meta-analysis for psychiatric research using free software R. *Shanghai Archives of Psychiatry*. 2015 Jun;27(3):195-9. PMID: 2015-36530-010 **Ineligible study design**
158. Chen G, Henter ID, Manji HK. Looking ahead: Electroretinographic anomalies, glycogen synthase kinase-3, and biomarkers for neuropsychiatric disorders. *Biological Psychiatry*. 2014 15, 2014;76(2):86-8. doi: <http://dx.doi.org/10.1016/j.biopsych.2014.05.005>. **Ineligible study design**
159. Chen PS, Chang HH, Huang CC, et al. A longitudinal study of the association between the GNB3 C825T polymorphism and metabolic disturbance in bipolar II patients treated with valproate. *Pharmacogenomics Journal*. 2017 01 Mar;17(2):155-61. doi: <http://dx.doi.org/10.1038/tpj.2015.96>. PMID: 608296835 **Ineligible intervention**
160. Chen Y, Bobo WV, Watts K, et al. Comparative effectiveness of switching antipsychotic drug treatment to aripiprazole or ziprasidone for improving metabolic profile and atherogenic dyslipidemia: a 12-month, prospective, open-label study. *Journal of Psychopharmacology*. 2012 Sep;26(9):1201-10. doi: <http://dx.doi.org/10.1177/0269881111430748>. PMID: 22234928 **Bipolar not analyzed separately**

161. Chengappa KN, Baker RW, Shao L, et al. Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania. *Bipolar Disorders*. 2003 Feb;5(1):1-5. PMID: 12656931 **Over 50% dropout rate**
162. Chengappa KN, Levine J, Gershon S, et al. Inositol as an add-on treatment for bipolar depression. *Bipolar Disorders*. 2000 Mar;2(1):47-55. PMID: 11254020 **No eligible outcomes reported**
163. Chiang KJ, Tsai JC, Liu D, et al. Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: A metaanalysis of randomized controlled trials. *PLoS ONE*. 2017 May;12 (5) (no pagination)(e0176849)doi: <http://dx.doi.org/10.1371/journal.pone.0176849>. PMID: 615955928 **Ineligible study design**
164. Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *International Clinical Psychopharmacology*. 2012 Mar;27(2):76-90. doi: <http://dx.doi.org/10.1097/YIC.0b013e32834e4c56>. PMID: 22107783 **Ineligible study design**
165. Chou JC, Czobor P, Charles O, et al. Acute mania: haloperidol dose and augmentation with lithium or lorazepam. *Journal of Clinical Psychopharmacology*. 1999 Dec;19(6):500-5. PMID: 10587284 **Over 50% dropout rate**
166. Chou JC, Czobor P, Tuma I, et al. Pretreatment plasma HVA and haloperidol response in acute mania. *Journal of Affective Disorders*. 2000 Jul;59(1):55-9. PMID: 10814771 **No eligible outcomes reported**
167. Chou JCY. Review and update of the American Psychiatric Association practice guideline for bipolar disorder. *Primary Psychiatry*. 2004 2004;11(9):73-84. **Ineligible study design**
168. Chou JCY, Czobor P, Tuma I, et al. Pretreatment plasma HVA and haloperidol response in acute mania. *Journal of Affective Disorders*. 2000 2000;59(1):55-9. doi: <http://dx.doi.org/10.1016/S0165-0327%2899%2900134-2>. **No eligible outcomes reported**
169. Chue P, Kovacs CS. Safety and tolerability of atypical antipsychotics in patients with bipolar disorder: prevalence, monitoring and management. *Bipolar Disorders*. 2003;5 Suppl 2:62-79. PMID: 14700015 **Ineligible study design**
170. Chwieduk CM, Scott LJ. Asenapine: a review of its use in the management of mania in adults with bipolar I disorder. *CNS Drugs*. 2011 Mar;25(3):251-67. doi: <http://dx.doi.org/10.2165/11206700-000000000-00000>. PMID: 21323396 **Ineligible study design**
171. Ciapparelli A, Dell'Osso L, Tundo A, et al. Electroconvulsive therapy in medication-nonresponsive patients with mixed mania and bipolar depression. *Journal of Clinical Psychiatry*. 2001 Jul;62(7):552-5. PMID: 11488367 **Ineligible study design**
172. Cipriani A, Barbui C, Rendell J, et al. Clinical and regulatory implications of active run-in phases in long-term studies for bipolar disorder. *Acta Psychiatrica Scandinavica*. 2014 May;129(5):328-42. doi: <http://dx.doi.org/10.1111/acps.12223>. PMID: 24289821 **Ineligible study design**
173. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011 Oct 8;378(9799):1306-15. doi: [http://dx.doi.org/10.1016/S0140-6736\(11\)60873-8](http://dx.doi.org/10.1016/S0140-6736(11)60873-8). PMID: 21851976 **Ineligible study design**

174. Cipriani A, Hawton K, Stockton S, et al. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013;346:f3646. doi: <http://dx.doi.org/10.1136/bmj.f3646>. PMID: 23814104 **Ineligible study design**
175. Cipriani A, Rendell J, Geddes JR. Olanzapine in the long-term treatment of bipolar disorder: a systematic review and meta-analysis. *Journal of Psychopharmacology*. 2010 Dec;24(12):1729-38. doi: <http://dx.doi.org/10.1177/0269881109106900>. PMID: 19828571 **Ineligible study design**
176. Cipriani A, Rendell JM, Geddes J. Olanzapine in long-term treatment for bipolar disorder. *Cochrane Database of Systematic Reviews*. 2009(1):CD004367. doi: <http://dx.doi.org/10.1002/14651858.CD004367.pub2>. PMID: 19160237 **Ineligible study design**
177. Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2006(3):CD004362. PMID: 16856043 **Ineligible study design**
178. Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *International Journal of Clinical Practice*. 2009 Dec;63(12):1762-84. doi: <http://dx.doi.org/10.1111/j.1742-1241.2009.02228.x>. PMID: 19840150 **Ineligible study design**
179. Citrome L. Ziprasidone HCl capsules for the adjunctive maintenance treatment of bipolar disorder in adults. *Expert Review of Neurotherapeutics*. 2010 2010;10(7):1031-7. doi: <http://dx.doi.org/10.1586/ern.10.66>. **Duplicate reference**
180. Citrome L, Holt RI, Walker DJ, et al. Weight gain and changes in metabolic variables following olanzapine treatment in schizophrenia and bipolar disorder. *Clinical Drug Investigation*. 2011;31(7):455-82. doi: <http://dx.doi.org/10.2165/11589060-000000000-00000>. PMID: 21495734 **Ineligible study design**
181. Citrome L, Kantrowitz JT. Olanzapine dosing above the licensed range is more efficacious than lower doses: Fact or fiction? [References]. *Expert Review of Neurotherapeutics*. 2009 2009;9(7):1045-58. doi: <http://dx.doi.org/10.1586/ern.09.54>. **Ineligible study design**
182. Citrome L, Ketter TA, Cucchiaro J, et al. Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Journal of Affective Disorders*. Oct. 2013 28, 2013(Pagination)doi: <http://dx.doi.org/10.1016/j.jad.2013.10.040>. **No eligible outcomes reported**
183. Clarkin JF, Carpenter D, Hull J, et al. Effects of psychoeducational intervention for married patients with bipolar disorder and their spouses. *Psychiatric Services*. 1998 Apr;49(4):531-3. PMID: 9550248 **Bipolar not analyzed separately**
184. Colom F, Pacchiarotti I, Vieta E. Treatment arsenal for bipolar disorders: The role of psychoeducation in good clinical practice. *Psichiatria e Psicoterapia*. 2006 2006;25(1):3-6. **Ineligible study design**
185. Colom F, Vieta E, Martinez A, et al. What is the role of psychotherapy in the treatment of bipolar disorder? *Psychotherapy & Psychosomatics*. 1998;67(1):3-9. PMID: 9491434 **Ineligible study design**

186. Colom F, Vieta E, Sanchez-Moreno J, et al. Psychoeducation for bipolar II disorder: an exploratory, 5-year outcome subanalysis. *Journal of Affective Disorders*. 2009 Jan;112(1-3):30-5. doi: <http://dx.doi.org/10.1016/j.jad.2008.03.023>. PMID: 18486237 **Less than 11 subjects per arm**
187. Colom F, Vieta E, Sanchez-Moreno J, et al. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. *Bipolar Disorders*. 2005;7 Suppl 5:32-6. PMID: 16225558 **No eligible outcomes reported**
188. Colom F, Vieta E, Sanchez-Moreno J, et al. Psychoeducation in bipolar patients with comorbid personality disorders. *Bipolar Disorders*. 2004 Aug;6(4):294-8. PMID: 15225146 **Ineligible intervention**
189. Colombo C, Benedetti F, Barbini B, et al. Rate of switch from depression into mania after therapeutic sleep deprivation in bipolar depression. *Psychiatry Research*. 1999 Jun 30;86(3):267-70. PMID: 10482346 **Ineligible study design**
190. Colombo C, Lucca A, Benedetti F, et al. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. *Psychiatry Research*. 2000 Jul 24;95(1):43-53. PMID: 10904122 **Ineligible study design**
191. Connolly KR, Helmer A, Cristancho MA, et al. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. *Journal of Clinical Psychiatry*. 2012 Apr;73(4):e567-73. doi: <http://dx.doi.org/10.4088/JCP.11m07413>. PMID: 22579164 **Ineligible study design**
192. Cook JA, Copeland ME, Jonikas JA, et al. Results of a randomized controlled trial of mental illness self-management using Wellness Recovery Action Planning. *Schizophrenia Bulletin*. 2012 Jun;38(4):881-91. doi: <http://dx.doi.org/10.1093/schbul/sbr012>. PMID: 21402724 **Bipolar not analyzed separately**
193. Cookson J, Elliott B. The use of anticonvulsants in the aftermath of mania. *Journal of Psychopharmacology*. 2006 Mar;20(2 Suppl):23-30. PMID: 16551669 **Ineligible study design**
194. Correll CU. The role of antipsychotics and mood stabilizers in the treatment of bipolar disorder. *Giornale Italiano di Psicopatologia / Italian Journal of Psychopathology*. 2011 2011;17(3):341-51. **Ineligible study design**
195. Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disorders*. 2010 Mar;12(2):116-41. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00798.x>. PMID: 20402706 **Ineligible study design**
196. Coryell W. Maintenance treatment in bipolar disorder: a reassessment of lithium as the first choice. *Bipolar Disorders*. 2009 Jun;11 Suppl 2:77-83. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00712.x>. PMID: 19538687 **Ineligible study design**
197. Coryell W, Leon AC, Turvey C, et al. The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. *Journal of Affective Disorders*. 2001 Dec;67(1-3):79-88. PMID: 11869754 **Bipolar not analyzed separately**

198. Coryell W, Winokur G, Solomon D, et al. Lithium and recurrence in a long-term follow-up of bipolar affective disorder. *Psychological Medicine*. 1997 Mar;27(2):281-9. PMID: 9089821 **No eligible outcomes reported**
199. Costa RT, Cheniaux E, Range BP, et al. Group cognitive behavior therapy for bipolar disorder can improve the quality of life. *Brazilian Journal of Medical & Biological Research*. 2012 Sep;45(9):862-8. PMID: 22735175 **No eligible outcomes reported**
200. Costa RT, Cheniaux E, Rosaes PA, et al. The effectiveness of cognitive behavioral group therapy in treating bipolar disorder: a randomized controlled study. *Revista Brasileira de Psiquiatria*. 2011 Jun;33(2):144-9. PMID: 21829907 **No eligible outcomes reported**
201. Cousins DA, Young AH. The armamentarium of treatments for bipolar disorder: a review of the literature. *International Journal of Neuropsychopharmacology*. 2007 Jun;10(3):411-31. PMID: 17176493 **Ineligible study design**
202. Cramer JA, Rosenheck R. Enhancing medication compliance for people with serious mental illness. *Journal of Nervous & Mental Disease*. 1999 Jan;187(1):53-5. PMID: 9952254 **No eligible outcomes reported**
203. Crane CA, Hawes SW, Devine S, et al. Axis I psychopathology and the perpetration of intimate partner violence. *Journal of Clinical Psychology*. 2014 Mar;70(3):238-47. doi: <http://dx.doi.org/10.1002/jclp.22013>. PMID: 23824500 **Not treating bipolar**
204. Crowe M, Inder M, Carlyle D, et al. Nurse-led delivery of specialist supportive care for bipolar disorder: a randomized controlled trial. *Journal of Psychiatric & Mental Health Nursing*. 2012 Jun;19(5):446-54. doi: <http://dx.doi.org/10.1111/j.1365-2850.2011.01822.x>. PMID: 22070452 **Over 50% dropout rate**
205. Cruz N, Sanchez-Moreno J, Torres F, et al. Efficacy of modern antipsychotics in placebo-controlled trials in bipolar depression: a meta-analysis. *International Journal of Neuropsychopharmacology*. 2010 Feb;13(1):5-14. doi: <http://dx.doi.org/10.1017/S1461145709990344>. PMID: 19638254 **Ineligible study design**
206. Cuomo I, Motta P, Fini C, et al. The efficacy of asenapine in the treatment of bipolar disorder: A naturalistic longitudinal study indicating a favourable response in patients with substance abuse comorbidity. *European Psychiatry*. 2015 31 Mar;30:1152. **Ineligible study design**
207. Curtin F, Schulz P. Clonazepam and lorazepam in acute mania: a Bayesian meta-analysis. *Journal of Affective Disorders*. 2004 Mar;78(3):201-8. PMID: 15013244 **Ineligible study design**
208. Daglas R, Cotton SM, Allott K, et al. A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2016 Jan;31:20-8. doi: <http://dx.doi.org/10.1016/j.eurpsy.2015.09.460>. PMID: 26655594 **No eligible outcomes reported**
209. Dalum HS, Korsbek L, Mikkelsen JH, et al. Illness management and recovery (IMR) in Danish community mental health centres. *Trials [Electronic Resource]*. 2011;12:195. doi: <http://dx.doi.org/10.1186/1745-6215-12-195>. PMID: 21849024 **Ineligible study design**

210. Dardennes R, Even C, Bange F, et al. Comparison of carbamazepine and lithium in the prophylaxis of bipolar disorders. A meta-analysis. *British Journal of Psychiatry*. 1995 Mar;166(3):378-81. PMID: 7788131 **Ineligible study design**
211. Datto C, Pottorf WJ, Feeley L, et al. Bipolar II compared with bipolar I disorder: Baseline characteristics and treatment response to quetiapine in a pooled analysis of five placebo-controlled clinical trials of acute bipolar depression. *Annals of General Psychiatry*. 2016 March 11;15 (1) (no pagination)(9)doi: <http://dx.doi.org/10.1186/s12991-016-0096-0>. PMID: 608914705 **No eligible outcomes reported**
212. Dauphinais DR, Rosenthal JZ, Terman M, et al. Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry Research*. 2012 Mar 30;196(1):57-61. doi: <http://dx.doi.org/10.1016/j.psychres.2012.01.015>. PMID: 22424890 **Ineligible study design**
213. de Azevedo Cardoso T, de Azambuja Farias C, Mondin TC, et al. Brief psychoeducation for bipolar disorder: Impact on quality of life in young adults in a 6-month follow-up of a randomized controlled trial. *Psychiatry Research*. 2014 30, 2014;220(3):896-902. doi: <http://dx.doi.org/10.1016/j.psychres.2014.09.013>. PMID: 25300245 **Over 50% dropout rate**
214. De Azevedo Cardoso T, Mondin TC, Reyes AN, et al. Biological rhythm and bipolar disorder: Twelve-month follow-up of a randomized clinical trial. *Journal of Nervous and Mental Disease*. 2015;203(10):792-7. doi: <http://dx.doi.org/10.1097/NMD.0000000000000369>. PMID: 2015431675 **Over 50% dropout rate**
215. De Fruyt J, Deschepper E, Audenaert K, et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. *Journal of Psychopharmacology*. 2012 May;26(5):603-17. doi: <http://dx.doi.org/10.1177/0269881111408461>. PMID: 21940761 **Ineligible study design**
216. de Macedo-Soares MB, Moreno RA, Rigonatti SP, et al. Efficacy of Electroconvulsive Therapy in Treatment-Resistant Bipolar Disorder: A Case Series. *The Journal of ECT*. 2005 2005;21(1):31-4. doi: <http://dx.doi.org/10.1097/01.yct.0000148621.88104.f1>. **Ineligible study design**
217. Deberdt W, Winokur A, Cavazzoni PA, et al. Amantadine for weight gain associated with olanzapine treatment. *European Neuropsychopharmacology*. 2005 2005;15(1):13-21. doi: <http://dx.doi.org/10.1016/j.euroneuro.2004.03.005>. PMID: 15572269 **Bipolar not analyzed separately**
218. Deckersbach T, Holzel BK, Eisner LR, et al. Mindfulness-based cognitive therapy for nonremitted patients with bipolar disorder. *CNS Neuroscience & Therapeutics*. 2012 Feb;18(2):133-41. doi: <http://dx.doi.org/10.1111/j.1755-5949.2011.00236.x>. PMID: 22070469 **Ineligible study design**
219. Deckersbach T, Nierenberg AA, Kessler R, et al. RESEARCH: Cognitive rehabilitation for bipolar disorder: An open trial for employed patients with residual depressive symptoms. *CNS Neuroscience & Therapeutics*. 2010 Oct;16(5):298-307. doi: <http://dx.doi.org/10.1111/j.1755-5949.2009.00110.x>. PMID: 19895584 **Ineligible study design**
220. Deckersbach T, Nierenberg AA, McInnis MG, et al. Baseline disability and poor functioning in bipolar disorder predict worse outcomes: results from the Bipolar CHOICE study. *Journal of Clinical Psychiatry*. 2016 Jan;77(1):100-8. doi: <http://dx.doi.org/10.4088/JCP.14m09210>. PMID: 26845265 **Ineligible study design**

221. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. *Clinical Therapeutics*. 2004 May;26(5):649-66. PMID: 15220010 **Ineligible study design**
222. Dell'Osso B, Mundo E, D'Urso N, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disorders*. 2009 Feb;11(1):76-81. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00651.x>. PMID: 19133969 **Ineligible study design**
223. Dell'osso B, Timtim S, Hooshmand F, et al. Superior chronic tolerability of adjunctive modafinil compared to pramipexole in treatment-resistant bipolar disorder. *Journal of Affective Disorders*. 2013 Aug 15;150(1):130-5. doi: <http://dx.doi.org/10.1016/j.jad.2012.11.030>. PMID: 23261131 **Ineligible study design**
224. Demant KM, Vinberg M, Kessing LV, et al. Effects of short-term cognitive remediation on cognitive dysfunction in partially or fully remitted individuals with bipolar disorder: Results of a randomised controlled trial. *PLoS ONE*. 2015 12 Jun;10(6)doi: <http://dx.doi.org/10.1371/journal.pone.0127955>. PMID: 2015178422 **No eligible outcomes reported**
225. Denicoff KD, Smith-Jackson EE, Disney ER, et al. Comparative prophylactic efficacy of lithium, carbamazepine, and the combination in bipolar disorder. *Journal of Clinical Psychiatry*. 1997 Nov;58(11):470-8. PMID: 9413412 **Ineligible study design**
226. Dennehy EB, Schnyer R, Bernstein IH, et al. The safety, acceptability, and effectiveness of acupuncture as an adjunctive treatment for acute symptoms in bipolar disorder. *Journal of Clinical Psychiatry*. 2009 Jun;70(6):897-905. doi: <http://dx.doi.org/10.4088/JCP.08m04208>. PMID: 19422756 **Less than 11 subjects per arm**
227. Depp CA, Bowie CR, Mausbach BT, et al. Current smoking is associated with worse cognitive and adaptive functioning in serious mental illness. *Acta Psychiatrica Scandinavica*. 2015 May;131(5):333-41. doi: <http://dx.doi.org/10.1111/acps.12380>. PMID: 25559296 **Ineligible study design**
228. Depp CA, Lebowitz BD, Patterson TL, et al. Medication adherence skills training for middle-aged and elderly adults with bipolar disorder: development and pilot study. *Bipolar Disorders*. 2007 Sep;9(6):636-45. PMID: 17845279 **Ineligible study design**
229. Depp CA, Mausbach B, Granholm E, et al. Mobile interventions for severe mental illness: design and preliminary data from three approaches. *Journal of Nervous & Mental Disease*. 2010 Oct;198(10):715-21. doi: <http://dx.doi.org/10.1097/NMD.0b013e3181f49ea3>. PMID: 20921861 **Ineligible study design**
230. Der-Hacopian E. Motivations for alcohol consumption among individuals diagnosed with bipolar disorder. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2014;74(8-B(E)) **Ineligible study design**
231. Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomised trials. *BMC Psychiatry*. 2007;7:40. PMID: 17705840 **Ineligible study design**
232. Deshauer D, Fergusson D, Duffy A, et al. Re-evaluation of randomized control trials of lithium monotherapy: a cohort effect. *Bipolar Disorders*. 2005 Aug;7(4):382-7. PMID: 16026492 **Ineligible study design**

233. Dogan S, Sabanciogullari S. The effects of patient education in lithium therapy on quality of life and compliance. *Archives of Psychiatric Nursing*. 2003 Dec;17(6):270-5. PMID: 14685951 **Ineligible study design**
234. Dolberg OT, Dannon PN, Schreiber S, et al. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disorders*. 2002;4 Suppl 1:94-5. PMID: 12479689 **Ineligible study design**
235. Dopheide JA, Wincor MZ. Gabapentin and lamotrigine in the treatment of bipolar disorder. *Journal of the American Pharmaceutical Association*. 1998 Sep-Oct;38(5):632-4. PMID: 9782699 **Ineligible study design**
236. Drake RE, Frey W, Bond GR, et al. Assisting Social Security Disability Insurance beneficiaries with schizophrenia, bipolar disorder, or major depression in returning to work. *American Journal of Psychiatry*. 2013 Dec 1;170(12):1433-41. doi: <http://dx.doi.org/10.1176/appi.ajp.2013.13020214>. PMID: 23929355 **Ineligible intervention**
237. Dratcu L, Bobmanuel S, Davies W, et al. A UK panel consensus on the initiation of aripiprazole for the treatment of bipolar mania. *International Journal of Psychiatry in Clinical Practice*. 2012 Oct;16(4):244-58. doi: <http://dx.doi.org/10.3109/13651501.2012.709865>. PMID: 22809129 **Ineligible study design**
238. Dubovsky SL. Group therapy effective for bipolar disorder. Education-based therapy may help avert relapses. *Health News*. 2003 Jun;9(6):4. PMID: 12793397 **Ineligible study design**
239. Dubovsky SL. Treatment of bipolar depression. *Psychiatric Clinics of North America*. 2005 Jun;28(2):349-70, vii. PMID: 15826736 **Ineligible study design**
240. Ducharme S, Murray ED, Seiner SJ, et al. Retrospective Analysis of the Short-Term Safety of ECT in Patients With Neurological Comorbidities: A Guide for Pre-ECT Neurological Evaluations. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2015;27(4):311-21. doi: <http://dx.doi.org/10.1176/appi.neuropsych.14080195>. PMID: 25658682 **No eligible outcomes reported**
241. Dukart J, Regen F, Kherif F, et al. Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. *Proceedings of the National Academy of Sciences of the United States of America*. 2014 Jan 21;111(3):1156-61. doi: <http://dx.doi.org/10.1073/pnas.1321399111>. PMID: 24379394 **Bipolar not analyzed separately**
242. Duncan D, McConnell HW, Taylor D. Lamotrigine in bipolar affective disorder. *Psychiatric Bulletin*. 1998 1998;22(10):630-2. doi: <http://dx.doi.org/10.1192/pb.22.10.630>. **Ineligible study design**
243. Dunner DL. Safety and tolerability of emerging pharmacological treatments for bipolar disorder. *Bipolar Disorders*. 2005 2005;7(4):307-25. doi: <http://dx.doi.org/10.1111/j.1399-5618.2005.00235.x>. **Ineligible study design**
244. Durgam S, Earley W, Lipschitz A, et al. An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression. *American Journal of Psychiatry*. 2016 Mar 1;173(3):271-81. doi: <http://dx.doi.org/10.1176/appi.ajp.2015.15020164>. PMID: 26541814 **Ineligible study design**

245. Earley W, Durgam S, Lu K, et al. Tolerability of cariprazine in the treatment of acute bipolar I mania: A pooled post hoc analysis of 3 phase II/III studies. *Journal of Affective Disorders*. 2017 01 Jun;215:205-12. doi: <http://dx.doi.org/10.1016/j.jad.2017.03.032>. PMID: 614950830 **Duplicate reference**
246. Ebert D, Jaspert A, Murata H, et al. Initial lithium augmentation improves the antidepressant effects of standard TCA treatment in non-resistant depressed patients. *Psychopharmacology*. 1995 Mar;118(2):223-5. PMID: 7617812 **No eligible outcomes reported**
247. Eden Evins A, Demopulos C, Nierenberg A, et al. A double-blind, placebo-controlled trial of adjunctive donepezil in treatment-resistant mania. *Bipolar Disorders*. 2006 Feb;8(1):75-80. PMID: 16411983 **Fewer than 11 subjects per arm**
248. Eden Evins A, Demopulos C, Yovel I, et al. Inositol augmentation of lithium or valproate for bipolar depression. *Bipolar Disorders*. 2006 Apr;8(2):168-74. PMID: 16542187 **Ineligible study design**
249. Ekman M, Lindgren P, Miltenburger C, et al. Cost effectiveness of quetiapine in patients with acute bipolar depression and in maintenance treatment after an acute depressive episode. *Pharmacoeconomics*. 2012 Jun 1;30(6):513-30. doi: <http://dx.doi.org/10.2165/11594930-000000000-00000>. PMID: 22591130 **Ineligible study design**
250. El Haddad M, Houben R, Berte B, et al. Bipolar electrograms characteristics at the left atrial-pulmonary vein junction: Toward a new algorithm for automated verification of pulmonary vein isolation. *Heart Rhythm*. 2015 Jan;12(1):21-31. doi: <http://dx.doi.org/10.1016/j.hrthm.2014.08.030>. PMID: 25240694 **Not bipolar disorder**
251. El Mallakh RS, Vieta E, Rollin L, et al. A comparison of two fixed doses of aripiprazole with placebo in acutely relapsed, hospitalized patients with bipolar disorder I (manic or mixed) in subpopulations (CN138-007). *European Neuropsychopharmacology*. 2010 Nov;20(11):776-83. doi: <http://dx.doi.org/10.1016/j.euroneuro.2010.07.003>. PMID: 20728318 **Over 50% dropout rate**
252. El-Mallakh R, Vohringer P, Ostacher M, et al. Erratum: Antidepressants worsen rapid-cycling course in bipolar disorder: A STEP-BD randomized clinical trial (*Journal of Affective Disorders* (2015)). *Journal of Affective Disorders*. 2016 15 Jan;190:895. doi: <http://dx.doi.org/10.1016/j.jad.2015.08.015>. PMID: 605789134 **Fewer than 11 subjects per arm**
253. El-Mallakh R, Weisler RH, Townsend MH, et al. Bipolar II disorder: current and future treatment options. *Annals of Clinical Psychiatry*. 2006 Oct-Dec;18(4):259-66. PMID: 17162626 **Ineligible study design**
254. El-Mallakh RS. Medication adherence and the use of long-acting antipsychotics in bipolar disorder. *Journal of Psychiatric Practice*. 2007 Mar;13(2):79-85. PMID: 17414683 **Ineligible study design**
255. El-Mallakh RS, Ghaemi SN, Sagduyu K, et al. Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients. *Journal of Affective Disorders*. 2008 Dec;111(2-3):372-7. doi: <http://dx.doi.org/10.1016/j.jad.2008.03.025>. PMID: 18565592 **No eligible outcomes reported**
256. El-Mallakh RS, Ketter TA, Weisler RH, et al. Switching from other agents to extended-release carbamazepine in acute mania. *Psychopharmacology Bulletin*. 2008;41(1):52-8. PMID: 18362871 **Ineligible study design**

257. El-Mallakh RS, Marcus R, Baudelet C, et al. A 40-week double-blind aripiprazole versus lithium follow-up of a 12-week acute phase study (total 52 weeks) in bipolar I disorder. *Journal of Affective Disorders*. 2012 Feb;136(3):258-66. doi: <http://dx.doi.org/10.1016/j.jad.2011.11.043>. PMID: 22209190 **Over 50% dropout rate**
258. El-Mallakh RS, Salem MR, Chopra A, et al. A blinded, randomized comparison of immediate-release and extended-release carbamazepine capsules in manic and depressed bipolar subjects. *Annals of Clinical Psychiatry*. 2010 Feb;22(1):3-8. PMID: 20196977 **6 Pediatric**
259. El-Mallakh RS, Salem MR, Chopra AS, et al. Adverse event load in bipolar participants receiving either carbamazepine immediate-release or extended-release capsules: a blinded, randomized study. *International Clinical Psychopharmacology*. 2009 May;24(3):145-9. doi: <http://dx.doi.org/10.1097/YIC.0b013e328329b199>. PMID: 19367153 **Over 50% dropout rate**
260. El-Mallakh RS, Vohringer PA, Ostacher MM, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *Journal of Affective Disorders*. 2015 Sep;184:318-21. doi: <http://dx.doi.org/10.1016/j.jad.2015.04.054>. PMID: 2015-34966-047 **Ineligible intervention**
261. El-Mallakh RS, Vohringer PA, Ostacher MM, et al. Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. *Journal of Affective Disorders*. 2015 04 Jul;184:318-21. doi: <http://dx.doi.org/10.1016/j.jad.2015.04.054>. PMID: 605067425 **Fewer than 11 subjects per arm**
262. Elmslie JL, Porter RJ, Joyce PR, et al. Carnitine does not improve weight loss outcomes in valproate-treated bipolar patients consuming an energy-restricted, low-fat diet. *Bipolar Disorders*. 2006 Oct;8(5 Pt 1):503-7. PMID: 17042889 **Ineligible study design**
263. Emilien G, Maloteaux JM, Seghers A, et al. Lithium compared to valproic acid and carbamazepine in the treatment of mania: a statistical meta-analysis. *European Neuropsychopharmacology*. 1996 Aug;6(3):245-52. PMID: 8880085 **Ineligible study design**
264. Emilien G, Septien L, Brisard C, et al. Bipolar disorder: how far are we from a rigorous definition and effective management? *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2007 Jun 30;31(5):975-96. PMID: 17459551 **Ineligible study design**
265. Endicott J, Rajagopalan K, Minkwitz M, et al. A randomized, double-blind, placebo-controlled study of quetiapine in the treatment of bipolar I and II depression: improvements in quality of life. *International Clinical Psychopharmacology*. 2007 Jan;22(1):29-37. PMID: 17159457 **No eligible outcomes reported**
266. Engstrom C, Astrom M, Nordqvist-Karlsson B, et al. Relationship between prophylactic effect of lithium therapy and family history of affective disorders. *Biological Psychiatry*. 1997 Sep 15;42(6):425-33. PMID: 9285078 **Ineligible study design**
267. Ernst CL, Goldberg JF. Antidepressant properties of anticonvulsant drugs for bipolar disorder. *Journal of Clinical Psychopharmacology*. 2003 Apr;23(2):182-92. PMID: 12640220 **Ineligible study design**
268. Evans S, Newton R, Higgins S. Nutritional intervention to prevent weight gain in patients commenced on olanzapine: a randomized controlled trial. *Australian & New Zealand Journal of Psychiatry*. 2005 Jun;39(6):479-86. PMID: 15943650 **Bipolar not analyzed separately**

269. Evins AE. Efficacy of newer anticonvulsant medications in bipolar spectrum mood disorders. *Journal of Clinical Psychiatry*. 2003;64 Suppl 8:9-14. PMID: 12892536 **Ineligible study design**
270. Fagan CS, Carmody TJ, McClintock SM, et al. The effect of cognitive functioning on treatment attendance and adherence in comorbid bipolar disorder and cocaine dependence. *Journal of Substance Abuse Treatment*. 2015 Feb;49:15-20. doi: <http://dx.doi.org/10.1016/j.jsat.2014.06.008>. PMID: 2014-33120-001 **Ineligible study design**
271. Fagiolini A, De Filippis S, Azzarelli O, et al. Intramuscular aripiprazole for the treatment of agitation in schizophrenia and bipolar disorder: From clinical research to clinical practice. *Journal of Psychopathology / Giornale di Psicopatologia*. 2013 2013;19(1):34-41. **Ineligible study design**
272. Fagiolini A, Frank E, Cherry CR, et al. Clinical indicators for the use of antidepressants in the treatment of bipolar I depression. *Bipolar Disorders*. 2002 Oct;4(5):277-82. PMID: 12479658 **Ineligible study design**
273. Fagiolini A, Frank E, Houck PR, et al. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. *Journal of Clinical Psychiatry*. 2002 Jun;63(6):528-33. PMID: 12088166 **Ineligible study design**
274. Fajutrao L, Paulsson B, Liu S, et al. Cost-effectiveness of quetiapine plus mood stabilizers compared with mood stabilizers alone in the maintenance therapy of bipolar I disorder: results of a Markov model analysis. *Clinical Therapeutics*. 2009 Jun;31 Pt 1:1456-68. doi: <http://dx.doi.org/10.1016/j.clinthera.2009.06.009>. PMID: 19698903 **Ineligible study design**
275. Farren CK, Mc Elroy S. Treatment response of bipolar and unipolar alcoholics to an inpatient dual diagnosis program. *Journal of Affective Disorders*. 2008 Mar;106(3):265-72. PMID: 17707085 **Not treating bipolar**
276. Faurholt-Jepsen M, Munkholm K, Frost M, et al. Electronic self-monitoring of mood using IT platforms in adult patients with bipolar disorder: A systematic review of the validity and evidence. *BMC Psychiatry*. 2016 15 Jan;16 (1) (no pagination)(7)doi: <http://dx.doi.org/10.1186/s12888-016-0713-0>. PMID: 607740398 **Ineligible study design**
277. Fava GA, Bartolucci G, Rafanelli C, et al. Cognitive-behavioral management of patients with bipolar disorder who relapsed while on lithium prophylaxis. *Journal of Clinical Psychiatry*. 2001 Jul;62(7):556-9. PMID: 11488368 **Ineligible study design**
278. Fava GA, Ruini C, Rafanelli C. Sequential treatment of mood and anxiety disorders. *Journal of Clinical Psychiatry*. 2005 Nov;66(11):1392-400. PMID: 16420076 **Ineligible study design**
279. Fenton C, Scott LJ. Risperidone: a review of its use in the treatment of bipolar mania. *CNS Drugs*. 2005;19(5):429-44. PMID: 15907153 **Ineligible study design**
280. Ferrier IN. Lamotrigine and gabapentin: Alternatives in the treatment of bipolar disorder. *Neuropsychobiology*. 1998;38(3):192-7. doi: <http://dx.doi.org/10.1159/000026536>. **Ineligible study design**

281. Ferrier IN. Developments in mood stabilisers. British Medical Bulletin. 2001;57:179-92. PMID: 11719917
Ineligible study design
282. Fiorillo A, Del Vecchio V, Luciano M, et al. Efficacy of psychoeducational family intervention for bipolar I disorder: A controlled, multicentric, real-world study. Journal of Affective Disorders. 2015 1, 2015;172:291-9. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.021>. PMID: 25451428 **No eligible outcomes reported**
283. Flood C, Byford S, Henderson C, et al. Joint crisis plans for people with psychosis: economic evaluation of a randomised controlled trial. BMJ: British Medical Journal. 2006 2006;333(7571):729. doi: <http://dx.doi.org/10.1136/bmj.38929.653704.55>. **Ineligible study design**
284. Forester B, Sajatovic M, Tsai J, et al. Long-term treatment with lurasidone in older adults with bipolar depression: Results of a 6 month open-label study. European Psychiatry. 2015 31 Mar;30:1134. PMID: 71930814 **Ineligible study design**
285. Forester B, Sajatovic M, Tsai J, et al. Efficacy and safety of long-term treatment with lurasidone in older adults with bipolar depression: Results of a 6 month open-label study. American Journal of Geriatric Psychiatry. 2015 March;1):S170-S1. PMID: 71814372 **Ineligible study design**
286. Forester BP, Harper DG, Georgakas J, et al. Antidepressant effects of open label treatment with coenzyme Q10 in geriatric bipolar depression. Journal of Clinical Psychopharmacology. 2015 Jun;35(3):338-40. doi: <http://dx.doi.org/10.1097/JCP.0000000000000326>. PMID: 2015-19762-024 **Ineligible study design**
287. Forleo GB, Di Biase L, Bharmi R, et al. Hospitalization rates and associated cost analysis of cardiac resynchronization therapy with an implantable defibrillator and quadripolar vs. bipolar left ventricular leads: a comparative effectiveness study. Europace. 2015 Jan;17(1):101-7. doi: <http://dx.doi.org/10.1093/europace/euu290>. PMID: 25371428 **Not bipolar disorder**
288. Fornaro M, McCarthy MJ, De Berardis D, et al. Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: A preliminary open label study. Neuropsychiatric Disease and Treatment. 2013 15, 2013;9:243-51. **Ineligible study design**
289. Fornaro M, Stubbs B, De Berardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: A systematic review and exploratory meta-analysis of placebo-controlled clinical trials. International Journal of Molecular Sciences. 2016;17(2)doi: <http://dx.doi.org/10.3390/ijms17020241>. PMID: 608342330 **Ineligible study design**
290. Fountoulakis KN. The contemporary face of bipolar illness: complex diagnostic and therapeutic challenges. Cns Spectrums. 2008 Sep;13(9):763-74, 77-9. PMID: 18849896 **Ineligible study design**
291. Fountoulakis KN, Gonda X, Vieta E, et al. Treatment of psychotic symptoms in bipolar disorder with aripiprazole monotherapy: A meta-analysis. Annals of General Psychiatry. 2009 31, 2009;8:27. doi: <http://dx.doi.org/10.1186/1744-859X-8-27>. **Ineligible study design**
292. Fountoulakis KN, Kasper S, Andreassen O, et al. Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. European Archives of Psychiatry & Clinical Neuroscience. 2012 Jun;262 Suppl 1:1-48. doi: <http://dx.doi.org/10.1007/s00406-012-0323-x>. PMID: 22622948
Ineligible study design

293. Fountoulakis KN, Kontis D, Gonda X, et al. Treatment of mixed bipolar states. *International Journal of Neuropsychopharmacology*. 2012 Aug;15(7):1015-26. doi: <http://dx.doi.org/10.1017/S1461145711001817>. PMID: 22217434 **Ineligible study design**
294. Fountoulakis KN, Kontis D, Gonda X, et al. A systematic review of the evidence on the treatment of rapid cycling bipolar disorder. *Bipolar Disorders*. 2013 Mar;15(2):115-37. doi: <http://dx.doi.org/10.1111/bdi.12045>. PMID: 23437958 **Ineligible study design**
295. Fountoulakis KN, Vieta E. Treatment of bipolar disorder: a systematic review of available data and clinical perspectives. *International Journal of Neuropsychopharmacology*. 2008 Nov;11(7):999-1029. doi: <http://dx.doi.org/10.1017/S1461145708009231>. PMID: 18752718 **Ineligible study design**
296. Fountoulakis KN, Vieta E. Efficacy and safety of aripiprazole in the treatment of bipolar disorder: A systematic review. *Annals of General Psychiatry*. 2009 27, 2009;8:16. doi: <http://dx.doi.org/10.1186/1744-859X-8-16>. **Ineligible study design**
297. Fountoulakis KN, Vieta E, Schmidt F. Aripiprazole monotherapy in the treatment of bipolar disorder: a meta-analysis. *Journal of Affective Disorders*. 2011 Oct;133(3):361-70. doi: <http://dx.doi.org/10.1016/j.jad.2010.10.018>. PMID: 21040979 **Ineligible study design**
298. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *British Journal of Psychiatry*. 2006 Jan;188:46-50. PMID: 16388069 **Ineligible intervention**
299. Frank E, Wallace ML, Hall M, et al. An integrated risk reduction intervention can reduce body mass index in individuals being treated for bipolar I disorder: Results from a randomized trial. *Bipolar Disorders*. 2015 Jun;17(4):424-37. doi: <http://dx.doi.org/10.1111/bdi.12283>. PMID: 2015-25546-007 **No eligible outcomes reported**
300. Frecska E, Kovacs AI, Balla P, et al. The message of the survival curves: I. Composite analysis of long-term treatment studies in bipolar disorder. *Neuropsychopharmacologia Hungarica*. 2012 Sep;14(3):155-64. PMID: 22987729 **Ineligible study design**
301. Fredman SJ, Baucom DH, Boeding SE, et al. Relatives' emotional involvement moderates the effects of family therapy for bipolar disorder. *Journal of Consulting and Clinical Psychology*. 2015 Feb;83(1):81-91. doi: <http://dx.doi.org/10.1037/a0037713>. PMID: 2014-37304-001 **Ineligible study design**
302. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. *American Journal of Psychiatry*. 1998 Jan;155(1):12-21. PMID: 9433333 **Ineligible study design**
303. Frye MA, Altshuler LL. Selection of initial treatment for bipolar disorder, manic phase. *Modern Problems of Pharmacopsychiatry*. 1997;25:88-113. PMID: 9344372 **Ineligible study design**
304. Frye MA, Amchin J, Bauer M, et al. Randomized, placebo-controlled, adjunctive study of armodafinil for bipolar I depression: implications of novel drug design and heterogeneity of concurrent bipolar maintenance treatments. *International Journal of Bipolar Disorders*. 2015 07 Dec;3(1)doi: <http://dx.doi.org/10.1186/s40345-015-0034-0>. **Ineligible study design**
305. Frye MA, Eudicone J, Pikalov A, et al. Aripiprazole efficacy in irritability and disruptive-aggressive symptoms: Young Mania Rating Scale line analysis from two, randomized, double-blind, placebo-

- controlled trials. *Journal of Clinical Psychopharmacology*. 2008 2008;28(2):243-5. doi: <http://dx.doi.org/10.1097/JCP.0b013e31816745f7>. **Ineligible study design**
306. Frye MA, Helleman G, McElroy SL, et al. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *American Journal of Psychiatry*. 2009 Feb;166(2):164-72. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.08030322>. PMID: 19015231 **No eligible outcomes reported**
 307. Frye MA, Ketter TA, Kimbrell TA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *Journal of Clinical Psychopharmacology*. 2000 2000;20(6):607-14. doi: <http://dx.doi.org/10.1097/00004714-200012000-00004>. **Bipolar not analyzed separately**
 308. Frye MA, McElroy SL, Prieto ML, et al. Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. *Journal of Clinical Psychiatry*. 2015 Feb;76(2):174-80. doi: <http://dx.doi.org/10.4088/JCP.14m09127>. PMID: 25611077 **No eligible outcomes reported**
 309. Frye MA, Yatham LN, Calabrese JR, et al. Incidence and time course of subsyndromal symptoms in patients with bipolar I disorder: an evaluation of 2 placebo-controlled maintenance trials. *Journal of Clinical Psychiatry*. 2006 Nov;67(11):1721-8. PMID: 17196051 **Ineligible study design**
 310. Fu DJ, Turkoz I, Bossie CA, et al. Rapid onset of treatment effects on psychosis, depression, and mania in patients with acute exacerbation of schizoaffective disorder following treatment with oral extended-release paliperidone. *Journal of Affective Disorders*. 2016 Mar 15;193:381-90. doi: <http://dx.doi.org/10.1016/j.jad.2015.12.060>. PMID: 26802315 **Over 20% schizoaffective**
 311. Furey ML, Drevets WC. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Archives of General Psychiatry*. 2006 Oct;63(10):1121-9. PMID: 17015814 **Bipolar not analyzed separately**
 312. Furey ML, Khanna A, Hoffman EM, et al. Scopolamine produces larger antidepressant and anti-anxiety effects in women than in men. *Neuropsychopharmacology*. 2010 Nov;35(12):2479-88. doi: <http://dx.doi.org/10.1038/npp.2010.131>. PMID: 20736989 **Bipolar not analyzed separately**
 313. Furey ML, Nugent AC, Speer AM, et al. Baseline mood-state measures as predictors of antidepressant response to scopolamine. *Psychiatry Research*. 2012 30, 2012;196(1):62-7. doi: <http://dx.doi.org/10.1016/j.psychres.2012.01.003>. **Ineligible study design**
 314. Gagne GG, Jr., Furman MJ, Carpenter LL, et al. Efficacy of continuation ECT and antidepressant drugs compared to long-term antidepressants alone in depressed patients. *American Journal of Psychiatry*. 2000 Dec;157(12):1960-5. PMID: 11097961 **Ineligible study design**
 315. Gajwani P, Kemp DE, Muzina DJ, et al. Acute treatment of mania: an update on new medications. *Current Psychiatry Reports*. 2006 Dec;8(6):504-9. PMID: 17094930 **Ineligible study design**
 316. Gallagher P, Malik N, Newham J, et al. Antiglucocorticoid treatments for mood disorders. *Cochrane Database of Systematic Reviews*. 2008(1):CD005168. doi: <http://dx.doi.org/10.1002/14651858.CD005168.pub2>. PMID: 18254070 **Not treating bipolar**
 317. Galvez V, Alonzo A, Martin D, et al. Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS). *Journal of ECT*. 2011 Sep;27(3):256-8. doi: <http://dx.doi.org/10.1097/YCT.0b013e3182012b89>. PMID: 21206371 **Ineligible study design**

318. Gao K, Calabrese JR. Newer treatment studies for bipolar depression. *Bipolar Disorders*. 2005;7 Suppl 5:13-23. PMID: 16225556 **Ineligible study design**
319. Gao K, Fang F, Wang Z, et al. Subjective Versus Objective Weight Gain during Acute Treatment with Second-Generation Antipsychotics in Schizophrenia and Bipolar Disorder. *Journal of Clinical Psychopharmacology*. 2016 01 Dec;36(6):637-42. doi: <http://dx.doi.org/10.1097/JCP.0000000000000596>. PMID: 612817049 **Ineligible study design**
320. Gao K, Gajwani P, Elhaj O, et al. Typical and atypical antipsychotics in bipolar depression. *Journal of Clinical Psychiatry*. 2005 Nov;66(11):1376-85. PMID: 16420074 **Ineligible study design**
321. Gao K, Kemp DE, Fein E, et al. Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. *Journal of Clinical Psychiatry*. 2011 Aug;72(8):1063-71. doi: <http://dx.doi.org/10.4088/JCP.09r05535gre>. PMID: 21034695 **Ineligible study design**
322. Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *Journal of Clinical Psychopharmacology*. 2008 Apr;28(2):203-9. doi: <http://dx.doi.org/10.1097/JCP.0b013e318166c4d5>. PMID: 18344731 **Ineligible study design**
323. Gao K, Kemp DE, Ganocy SJ, et al. Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disorders*. 2008 Dec;10(8):907-15. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00637.x>. PMID: 19594506 **No eligible outcomes reported**
324. Gao K, Muzina D, Gajwani P, et al. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. *Journal of Clinical Psychiatry*. 2006 Sep;67(9):1327-40. PMID: 17017818 **Ineligible study design**
325. Gao K, Pappadopulos E, Karayal ON, et al. Risk for adverse events and discontinuation due to adverse events of ziprasidone monotherapy relative to placebo in the acute treatment of bipolar depression, mania, and schizophrenia. *Journal of Clinical Psychopharmacology*. 2013 Jun;33(3):425-31. doi: <http://dx.doi.org/10.1097/JCP.0b013e3182917f3f>. PMID: 23609405 **Duplicate reference**
326. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol, lithium carbonate and their combination in the treatment of mania. *Journal of Affective Disorders*. 1980 12//;2(4):279-88. doi: [http://dx.doi.org/10.1016/0165-0327\(80\)90029-4](http://dx.doi.org/10.1016/0165-0327(80)90029-4). PMID: 6450787 **Fewer than 11 subjects per arm**
327. Gaudiano BA, Miller IW. Anxiety disorder comorbidity in Bipolar I Disorder: relationship to depression severity and treatment outcome. *Depression & Anxiety*. 2005;21(2):71-7. PMID: 15786484 **Ineligible study design**
328. Gaudiano BA, Uebelacker LA, Miller IW. Impact of remitted substance use disorders on the future course of bipolar I disorder: findings from a clinical trial. *Psychiatry Research*. 2008 Jul 15;160(1):63-71. doi: <http://dx.doi.org/10.1016/j.psychres.2007.05.014>. PMID: 18514326 **Ineligible study design**
329. Geddes JR, Burgess S, Hawton K, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *American Journal of Psychiatry*. 2004 Feb;161(2):217-22. PMID: 14754766 **Ineligible study design**

330. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *British Journal of Psychiatry*. 2009 Jan;194(1):4-9. doi: <http://dx.doi.org/10.1192/bjp.bp.107.048504>. PMID: 19118318 **No eligible outcomes reported**
- D2331. Geddes JR, Gardiner A, Rendell J, et al. Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine monotherapy (and folic acid versus placebo) in bipolar depression (CEQUEL): A 2 x 2 factorial randomised trial. *The Lancet Psychiatry*. 2016 01 Jan;3(1):31-9. doi: <http://dx.doi.org/10.1016/S2215-0366%2815%2900450-2>. PMID: 26687300 PMID/607320783 Embase **Over 50% dropout rate**
332. Gedge L, Lazowski L, Murray D, et al. Effects of quetiapine on sleep architecture in patients with unipolar or bipolar depression. *Neuropsychiatric Disease and Treatment*. 2010 10, 2010;6:501-8. **Ineligible study design**
333. Gentile S. Extrapyramidal adverse events associated with atypical antipsychotic treatment of bipolar disorder. *Journal of Clinical Psychopharmacology*. 2007 Feb;27(1):35-45. PMID: 17224710 **Ineligible study design**
334. George MS, Nahas Z, Molloy M, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry*. 2000 2000;48(10):962-70. doi: <http://dx.doi.org/10.1016/S0006-3223%2800%2901048-9>. **No eligible outcomes reported**
335. George MS, Padberg F, Schlaepfer TE, et al. Controversy: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-compulsive disorder, panic, posttraumatic stress disorder). *Brain Stimulation*. 2009 Jan;2(1):14-21. doi: <http://dx.doi.org/10.1016/j.brs.2008.06.001>. PMID: 20633399 **Ineligible study design**
336. Gergerlioglu HS, Savas HA, Bulbul F, et al. Changes in nitric oxide level and superoxide dismutase activity during antimanic treatment.[Erratum appears in *Prog Neuropsychopharmacol Biol Psychiatry*. 2007 Aug 15;31(6):1345]. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2007 Apr 13;31(3):697-702. PMID: 17303295 **Ineligible study design**
337. Gergerlioglu HS, Savas HA, Celik A, et al. Atypical antipsychotic usage-related higher serum leptin levels and disabled lipid profiles in euthymic bipolar patients. *Neuropsychobiology*. 2006;53(2):108-12. PMID: 16557041 **Ineligible study design**
338. Ghadiri Vasfi M, Moradi-Lakeh M, Esmaceli N, et al. Efficacy of aftercare services for people with severe mental disorders in Iran: a randomized controlled trial. *Psychiatric Services*. 2015 Apr 1;66(4):373-80. doi: <http://dx.doi.org/10.1176/appi.ps.201400111>. PMID: 25828982 **Over 20% schizoaffective**
339. Ghaemi SN, Goodwin FK. Use of atypical antipsychotic agents in bipolar and schizoaffective disorders: review of the empirical literature. *Journal of Clinical Psychopharmacology*. 1999 Aug;19(4):354-61. PMID: 10440464 **Ineligible study design**
340. Ghaemi SN, Hsu DJ, Rosenquist KJ, et al. Extrapyramidal side effects with atypical neuroleptics in bipolar disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2006 Mar;30(2):209-13. PMID: 16412546 **No eligible outcomes reported**

341. Ghaemi SN, Lenox MS, Baldessarini RJ. Effectiveness and safety of long-term antidepressant treatment in bipolar disorder. *Journal of Clinical Psychiatry*. 2001 Jul;62(7):565-9. PMID: 11488370 **Ineligible study design**
342. Ghaemi SN, Ostacher MM, El-Mallakh RS, et al. Antidepressant discontinuation in bipolar depression: a Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized clinical trial of long-term effectiveness and safety. *Journal of Clinical Psychiatry*. 2010 Apr;71(4):372-80. doi: <http://dx.doi.org/10.4088/JCP.08m04909gre>. PMID: 20409444 **Over 50% dropout rate**
343. Ghaemi SN, Wingo AP, Filkowski MA, et al. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatrica Scandinavica*. 2008 Nov;118(5):347-56. doi: <http://dx.doi.org/10.1111/j.1600-0447.2008.01257.x>. PMID: 18727689 **Ineligible study design**
344. Giannini AJ, Nakonecz AM, Melemis SM, et al. Magnesium oxide augmentation of verapamil maintenance therapy in mania. *Psychiatry Research*. 2000 Feb 14;93(1):83-7. PMID: 10699232 **Ineligible intervention**
345. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *American Journal of Psychiatry*. 2004 Sep;161(9):1537-47. PMID: 15337640 **Ineligible study design**
346. Gildengers A, Tatsuoka C, Bialko C, et al. Correlates of treatment response in depressed older adults with bipolar disorder. *Journal of Geriatric Psychiatry & Neurology*. 2012 Mar;25(1):37-42. doi: <http://dx.doi.org/10.1177/0891988712436685>. PMID: 22467845 **Ineligible study design**
347. Gitlin M, Frye MA. Maintenance therapies in bipolar disorders. *Bipolar Disorders*. 2012 May;14 Suppl 2:51-65. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.00992.x>. PMID: 22510036 **Ineligible study design**
348. Gliddon E, Lauder S, Berk L, et al. Evaluating discussion board engagement in the MoodSwings online self-help program for bipolar disorder: protocol for an observational prospective cohort study. *BMC Psychiatry*. 2015 Oct 14;15:243. doi: <http://dx.doi.org/10.1186/s12888-015-0630-7>. PMID: 26462799 **Ineligible study design**
349. Gnanadesikan M, Freeman MP, Gelenberg AJ. Alternatives to lithium and divalproex in the maintenance treatment of bipolar disorder. *Bipolar Disorders*. 2003 Jun;5(3):203-16. PMID: 12780874 **Ineligible study design**
350. Goikolea JM, Colom F, Torres I, et al. Lower rate of depressive switch following antimanic treatment with second-generation antipsychotics versus haloperidol. *Journal of Affective Disorders*. 2013 Jan 25;144(3):191-8. doi: <http://dx.doi.org/10.1016/j.jad.2012.07.038>. PMID: 23089129 **Ineligible study design**
351. Goldberg JF. What psychotherapists should know about pharmacotherapies for bipolar disorder. *Journal of Clinical Psychology*. 2007 May;63(5):475-90. PMID: 17417812 **Ineligible study design**
352. Goldberg JF, Bowden CL, Calabrese JR, et al. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. *Biological Psychiatry*. 2008 Jan 1;63(1):125-30. PMID: 17543894 **No eligible outcomes reported**

353. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *American Journal of Psychiatry*. 2004 Mar;161(3):564-6. PMID: 14992985 **Fewer than 11 subjects per arm**
354. Goldberg JF, Calabrese JR, Saville BR, et al. Mood stabilization and destabilization during acute and continuation phase treatment for bipolar I disorder with lamotrigine or placebo. *Journal of Clinical Psychiatry*. 2009 Sep;70(9):1273-80. doi: <http://dx.doi.org/10.4088/JCP.08m04381>. PMID: 19689918 **Over 50% dropout rate**
355. Goldberg JF, Nassir Ghaemi S. Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression. *Bipolar Disorders*. 2005;7 Suppl 5:3-12. PMID: 16225555 **Ineligible study design**
356. Goldberg JF, Perlis RH, Ghaemi SN, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *American Journal of Psychiatry*. 2007 Sep;164(9):1348-55. PMID: 17728419 **Ineligible study design**
357. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. *Bipolar Disorders*. 2003 Dec;5(6):407-20. PMID: 14636364 **Ineligible study design**
358. Goldstein MJ, Miklowitz DJ. Family intervention for persons with bipolar disorder. Hatfield, Agnes B [Ed]. 1994 **Ineligible study design**
359. Gonzalez Arnold J, Salcedo S, Ketter TA, et al. An exploratory study of responses to low-dose lithium in African Americans and Hispanics. *Journal of Affective Disorders*. 2015 Jun 1;178:224-8. doi: <http://dx.doi.org/10.1016/j.jad.2015.02.035>. PMID: 25827507 **Over 50% dropout rate**
360. Gonzalez JM, Bowden CL, Berman N, et al. One-year treatment outcomes of African-American and Hispanic patients with bipolar I or II disorder in STEP-BD. *Psychiatric Services*. 2010 Feb;61(2):164-72. doi: <http://dx.doi.org/10.1176/appi.ps.61.2.164>. PMID: 20123822 **Ineligible study design**
361. Gonzalez JM, Prihoda TJ. A case study of psychodynamic group psychotherapy for bipolar disorder. *American Journal of Psychotherapy*. 2007;61(4):405-22. **Ineligible study design**
362. Gonzalez S, Artal J, Gomez E, et al. Early intervention in bipolar disorder: the Jano program at Hospital Universitario Marques de Valdecilla. *Actas Espanolas de Psiquiatria*. 2012 Mar-Apr;40(2):51-6. PMID: 22508069 **Ineligible study design**
363. Gonzalez-Pinto A, Vieta E, Reed C, et al. Effectiveness of olanzapine monotherapy and olanzapine combination treatment in the long term following acute mania--results of a two year observational study in bipolar disorder (EMBLEM). *Journal of Affective Disorders*. 2011 Jun;131(1-3):320-9. doi: <http://dx.doi.org/10.1016/j.jad.2010.11.037>. PMID: 21195486 **Ineligible study design**
364. Goodnick PJ. Bipolar depression: a review of randomised clinical trials. *Expert Opinion on Pharmacotherapy*. 2007 Jan;8(1):13-21. PMID: 17163803 **Ineligible study design**
365. Goodwin FK. Rationale for long-term treatment of bipolar disorder and evidence for long-term lithium treatment. *Journal of Clinical Psychiatry*. 2002;63 Suppl 10:5-12. PMID: 12392347 **Ineligible study design**

366. Goodwin G, Vieta E. Effective maintenance treatment--breaking the cycle of bipolar disorder. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2005 Aug;20(5-6):365-71. PMID: 16122915 **Ineligible study design**
367. Goodwin GM, Bowden CL, Calabrese JR, et al. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *Journal of Clinical Psychiatry*. 2004 Mar;65(3):432-41. PMID: 15096085 **Ineligible study design**
368. Goodwin GM, Geddes JR. Latest maintenance data on lithium in bipolar disorder. *European Neuropsychopharmacology*. 2003 Aug;13 Suppl 2:S51-5. PMID: 12957720 **Ineligible study design**
369. Gopal S, Steffens DC, Kramer ML, et al. Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy. *Journal of Clinical Psychiatry*. 2005 Aug;66(8):1016-20. PMID: 16086617 **No eligible outcomes reported**
370. Goss AJ, Kaser M, Costafreda SG, et al. Modafinil augmentation therapy in unipolar and bipolar depression: a systematic review and meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry*. 2013 Nov;74(11):1101-7. doi: <http://dx.doi.org/10.4088/JCP.13r08560>. PMID: 24330897 **Ineligible study design**
371. Gouliaev G, Licht RW, Vestergaard P, et al. Treatment of manic episodes: zuclopenthixol and clonazepam versus lithium and clonazepam. *Acta Psychiatrica Scandinavica*. 1996 Feb;93(2):119-24. PMID: 8686481 **Bipolar not analyzed separately**
372. Grande I, Hidalgo-Mazzei D, Nieto E, et al. Asenapine prescribing patterns in the treatment of manic in- and outpatients: Results from the MANACOR study. *European Psychiatry*. 2015 Jun;30(4):528-34. doi: <http://dx.doi.org/10.1016/j.eurpsy.2015.01.003>. PMID: 2015-06676-001 **No eligible outcomes reported**
373. Grande I, Kapczinski F, Stertz L, et al. Peripheral brain-derived neurotrophic factor changes along treatment with extended release quetiapine during acute mood episodes: an open-label trial in drug-free patients with bipolar disorder. *Journal of Psychiatric Research*. 2012 Nov;46(11):1511-4. doi: <http://dx.doi.org/10.1016/j.jpsychires.2012.08.017>. PMID: 22939945 **No eligible outcomes reported**
374. Grande I, Vieta E. Pharmacotherapy of acute mania: Monotherapy or combination therapy with mood stabilizers and antipsychotics? *CNS Drugs*. 2015 Mar;29(3):221-7. doi: <http://dx.doi.org/10.1007/s40263-015-0235-1>. PMID: 2015-14036-005 **Ineligible study design**
375. Greenhalgh J, Knight C, Hind D, et al. Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies. *Health Technology Assessment (Winchester, England)*. 2005 Mar;9(9):1-156, iii-iv. PMID: 15774232 **Ineligible study design**
376. Gregory VL, Jr. Cognitive-behavioral therapy for depression in bipolar disorder: a meta-analysis. *Journal of Evidence-Based Social Work*. 2010 Jul;7(4):269-79. doi: <http://dx.doi.org/10.1080/15433710903176088>. PMID: 20799127 **Ineligible study design**

377. Grisaru N, Chudakov B, Yaroslavsky Y, et al. Transcranial magnetic stimulation in mania: a controlled study. *American Journal of Psychiatry*. 1998 Nov;155(11):1608-10. PMID: 9812128 **Ineligible study design**
378. Grunhaus L, Hirschman S, Dolberg OT, et al. Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. *Journal of ECT*. 2001 Jun;17(2):124-8. PMID: 11417923 **Ineligible intervention**
379. Grunhaus L, Schreiber S, Dolberg OT, et al. Response to ECT in major depression: are there differences between unipolar and bipolar depression? *Bipolar Disorders*. 2002;4 Suppl 1:91-3. PMID: 12479688 **Ineligible study design**
380. Grunze H. Lithium in the acute treatment of bipolar disorders-a stocktaking. *European Archives of Psychiatry & Clinical Neuroscience*. 2003 Jun;253(3):115-9. PMID: 12904974 **Ineligible study design**
381. Grunze H. Reevaluating therapies for bipolar depression. *Journal of Clinical Psychiatry*. 2005;66 Suppl 5:17-25. PMID: 16038598 **Ineligible study design**
382. Grunze H, Kotlik E, Costa R, et al. Assessment of the efficacy and safety of eslicarbazepine acetate in acute mania and prevention of recurrence: experience from multicentre, double-blind, randomised phase II clinical studies in patients with bipolar disorder I. *Journal of Affective Disorders*. 2015 Mar 15;174:70-82. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.013>. PMID: 25484179 **Over 50% dropout rate**
383. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania.[Erratum appears in *World J Biol Psychiatry*. 2009;10(3):255 Note: Dosage error in article text]. *World Journal of Biological Psychiatry*. 2009;10(2):85-116. doi: <http://dx.doi.org/10.1080/15622970902823202>. PMID: 19347775 **Ineligible study design**
384. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression. *World Journal of Biological Psychiatry*. 2010 Mar;11(2):81-109. doi: <http://dx.doi.org/10.3109/15622970903555881>. PMID: 20148751 **Ineligible study design**
385. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World Journal of Biological Psychiatry*. 2013 Apr;14(3):154-219. doi: <http://dx.doi.org/10.3109/15622975.2013.770551>. PMID: 23480132 **Ineligible study design**
386. Grunze H, Walden J. Relevance of new and newly rediscovered anticonvulsants for atypical forms of bipolar disorder. *Journal of Affective Disorders*. 2002 Dec;72 Suppl 1:S15-21. PMID: 12589899 **Ineligible study design**
387. Gu N, Wang G, Tan Q, et al. Efficacy and safety of quetiapine extended release monotherapy in bipolar depression: A multi-center, randomized, double-blind, placebo-controlled trial. *Psychopharmacology*. 2016 01 Apr;233(7):1289-97. doi: <http://dx.doi.org/10.1007/s00213-016-4215-z>. PMID: 608645719 **No eligible outcomes reported**

388. Gutierrez MJ, Scott J. Psychological treatment for bipolar disorders--a review of randomised controlled trials. *European Archives of Psychiatry & Clinical Neuroscience*. 2004 Apr;254(2):92-8. PMID: 15146338 **Ineligible study design**
389. Hadjipavlou G, Mok H, Yatham LN. Pharmacotherapy of bipolar II disorder: a critical review of current evidence. *Bipolar Disorders*. 2004 Feb;6(1):14-25. PMID: 14996137 **Ineligible study design**
390. Haghighi M, Bajoghli H, Bigdelou G, et al. Assessment of cognitive impairments and seizure characteristics in electroconvulsive therapy with and without sodium valproate in manic patients. *Neuropsychobiology*. 2013;67(1):14-24. doi: <http://dx.doi.org/10.1159/000343490>. PMID: 23221898 **No eligible outcomes reported**
391. Halaris A. Antiinflammatory augmentation strategy reverses treatment resistant bipolar depression. *Biological Psychiatry*. 2015 01 May;1):297S. PMID: 71846905 **Ineligible study design**
392. Harvey PD, Hassman H, Mao L, et al. Cognitive functioning and acute sedative effects of risperidone and quetiapine in patients with stable bipolar I disorder: a randomized, double-blind, crossover study. *Journal of Clinical Psychiatry*. 2007 Aug;68(8):1186-94. PMID: 17854242 **No eligible outcomes reported**
393. Hayes JF, Marston L, Walters K, et al. Lithium vs. valproate vs. olanzapine vs. quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. *World Psychiatry*. 2016 February;15(1):53-8. doi: <http://dx.doi.org/10.1002/wps.20298>. PMID: 611189425 **No eligible outcomes reported**
394. Hayes RD, Downs J, Chang CK, et al. The effect of clozapine on premature mortality: an assessment of clinical monitoring and other potential confounders. *Schizophrenia Bulletin*. 2015 May;41(3):644-55. doi: <http://dx.doi.org/10.1093/schbul/sbu120>. PMID: 25154620 **Over 20% schizoaffective**
395. Hayes RD, Downs J, Chang C-K, et al. The effect of clozapine on premature mortality: An assessment of clinical monitoring and other potential confounders. *Schizophrenia Bulletin*. 2015 May;41(3):644-55. doi: <http://dx.doi.org/10.1093/schbul/sbu120>. PMID: 2015-16497-014 **Bipolar not analyzed separately**
396. Henderson C, Flood C, Leese M, et al. Effect of joint crisis plans on use of compulsory treatment in psychiatry: single blind randomised controlled trial. *BMJ*. 2004 Jul 17;329(7458):136. PMID: 15240438 **Bipolar not analyzed separately**
397. Hennen J, Perlis RH, Sachs G, et al. Weight gain during treatment of bipolar I patients with olanzapine. *Journal of Clinical Psychiatry*. 2004 Dec;65(12):1679-87. PMID: 15641874 **Over 50% dropout rate**
398. Henriksen TE, Skrede S, Fasmer OB, et al. Blue-blocking glasses as additive treatment for mania: A randomized placebo-controlled trial. *Bipolar Disorders*. 2016 01 May;18(3):221-32. doi: <http://dx.doi.org/10.1111/bdi.12390>. PMID: 610504287 **Ineligible study design**
399. Himmerich H, Koethe D, Schuld A, et al. Plasma levels of leptin and endogenous immune modulators during treatment with carbamazepine or lithium. *Psychopharmacology*. 2005 May;179(2):447-51. PMID: 15565432 **Bipolar not analyzed separately**
400. Hirano J, Takamiya A, Yamagata B, et al. Frontal and temporal cortical functional recovery after electroconvulsive therapy for depression: A longitudinal functional near-infrared spectroscopy study. *Journal of Psychiatric Research*. 2017 01 Aug;91:26-35. doi: <http://dx.doi.org/10.1016/j.jpsychires.2017.02.018>. PMID: 614736995 **Ineligible study design**

401. Hirota T, Kishi T. Adenosine hypothesis in schizophrenia and bipolar disorder: A systematic review and meta-analysis of randomized controlled trial of adjuvant purinergic modulators. *Schizophrenia Research*. 2013 2013;149(1-3):88-95. doi: <http://dx.doi.org/10.1016/j.schres.2013.06.038>. **Ineligible study design**
402. Hirschfeld RM, Baker JD, Wozniak P, et al. The safety and early efficacy of oral-loaded divalproex versus standard-titration divalproex, lithium, olanzapine, and placebo in the treatment of acute mania associated with bipolar disorder. *Journal of Clinical Psychiatry*. 2003 Jul;64(7):841-6. PMID: 12934987 **No eligible outcomes reported**
403. Hirschfeld RM, Bowden CL, Vigna NV, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended-release in the acute treatment of mania. *Journal of Clinical Psychiatry*. 2010 Apr;71(4):426-32. doi: <http://dx.doi.org/10.4088/JCP.08m04960yel>. PMID: 20361904 **Over 50% dropout rate**
404. Hirschfeld RM, Kasper S. A review of the evidence for carbamazepine and oxcarbazepine in the treatment of bipolar disorder. *International Journal of Neuropsychopharmacology*. 2004 Dec;7(4):507-22. PMID: 15458610 **Ineligible study design**
405. Hirschfeld RM, Keck PE, Jr., Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. *American Journal of Psychiatry*. 2004 Jun;161(6):1057-65. PMID: 15169694 **Over 50% dropout rate**
406. Hirschfeld RM, Weisler RH, Raines SR, et al. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 2006 Mar;67(3):355-62. PMID: 16649820 **No eligible outcomes reported**
407. Hirschowitz J, Kolevzon A, Garakani A. The pharmacological treatment of bipolar disorder: the question of modern advances. *Harvard Review of Psychiatry*. 2010 Sep-Oct;18(5):266-78. doi: <http://dx.doi.org/10.3109/10673229.2010.507042>. PMID: 20825264 **Ineligible study design**
408. Hlastala SA, Frank E, Mallinger AG, et al. Bipolar depression: an underestimated treatment challenge. *Depression & Anxiety*. 1997;5(2):73-83. PMID: 9262937 **Ineligible study design**
409. Hollander E, Pallanti S, Allen A, et al. Does sustained-release lithium reduce impulsive gambling and affective instability versus placebo in pathological gamblers with bipolar spectrum disorders? *American Journal of Psychiatry*. 2005 Jan;162(1):137-45. PMID: 15625212 **Not treating bipolar**
410. Holloway F, Carson J. Intensive case management for the severely mentally ill. Controlled trial. *British Journal of Psychiatry*. 1998 Jan;172:19-22. PMID: 9534826 **Bipolar not analyzed separately**
411. Holmes MK, Erickson K, Luckenbaugh DA, et al. A comparison of cognitive functioning in medicated and unmedicated subjects with bipolar depression. *Bipolar Disorders*. 2008 Nov;10(7):806-15. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00628.x>. PMID: 19032712 **No eligible outcomes reported**

412. Holtzheimer PE, Kelley ME, Gross RE, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of General Psychiatry*. 2012 Feb;69(2):150-8. doi: <http://dx.doi.org/10.1001/archgenpsychiatry.2011.1456>. PMID: 22213770 **Ineligible study design**
413. Honig A, Arts BM, Ponds RW, et al. Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice. *International Clinical Psychopharmacology*. 1999 May;14(3):167-71. PMID: 10435769 **No eligible outcomes reported**
414. Honig A, Hofman A, Rozendaal N, et al. Psycho-education in bipolar disorder: effect on expressed emotion. *Psychiatry Research*. 1997 Aug 29;72(1):17-22. PMID: 9355815 **No eligible outcomes reported**
415. Hopkins HS, Gelenberg AJ. Serum lithium levels and the outcome of maintenance therapy of bipolar disorder. *Bipolar Disorders*. 2000 Sep;2(3 Pt 1):174-9. PMID: 11256684 **Ineligible study design**
416. Houston JP, Ahl J, Meyers AL, et al. Reduced suicidal ideation in bipolar I disorder mixed-episode patients in a placebo-controlled trial of olanzapine combined with lithium or divalproex. *Journal of Clinical Psychiatry*. 2006 Aug;67(8):1246-52. PMID: 16965203 **No eligible outcomes reported**
417. Huang CC, Wei IH. Unexpected interaction between quetiapine and valproate in patients with bipolar disorder. *General Hospital Psychiatry*. 2010 Jul-Aug;32(4):446.e1-2. doi: <http://dx.doi.org/10.1016/j.genhosppsych.2009.06.005>. PMID: 20633751 **Ineligible study design**
418. Hurley SC. Lamotrigine update and its use in mood disorders. *Annals of Pharmacotherapy*. 2002 May;36(5):860-73. PMID: 11978166 **Ineligible study design**
419. Husain MI, Chaudhry IB, Rahman RR, et al. Pilot study of a culturally adapted psychoeducation (CaPE) intervention for bipolar disorder in Pakistan. *International Journal of Bipolar Disorders*. 2017 01 Dec;5 (1) (no pagination)(3)doi: <http://dx.doi.org/10.1186/s40345-017-0074-8>. PMID: 614403784 **Ineligible study design**
420. Issakidis C, Sanderson K, Teesson M, et al. Intensive case management in Australia: A randomized controlled trial. *Acta Psychiatrica Scandinavica*. 1999 1999;99(5):360-7. doi: <http://dx.doi.org/10.1111/j.1600-0447.1999.tb07242.x>. **Bipolar not analyzed separately**
421. Ives-Deliperi VL, Howells F, Stein DJ, et al. The effects of mindfulness-based cognitive therapy in patients with bipolar disorder: A controlled functional MRI investigation. *Journal of Affective Disorders*. 2013 25, 2013;150(3):1152-7. doi: <http://dx.doi.org/10.1016/j.jad.2013.05.074>. **No eligible outcomes reported**
422. Jackson HJ, McGorry PD, Killackey E, et al. Acute-phase and 1-year follow-up results of a randomized controlled trial of CBT versus Befriending for first-episode psychosis: the ACE project. *Psychological Medicine*. 2008 May;38(5):725-35. PMID: 18005494 **Bipolar not analyzed separately**
423. Jahangard L, Haghighi M, Bigdelou G, et al. Comparing efficacy of ECT with and without concurrent sodium valproate therapy in manic patients. *Journal of ECT*. 2012 Jun;28(2):118-23. doi: <http://dx.doi.org/10.1097/YCT.0b013e31824b64b5>. PMID: 22531205 **No eligible outcomes reported**

424. Jainer AK, King M, Sridharan S, et al. New Perspectives in the Treatment of Bipolar Affective Disorder. *International Medical Journal*. 2005 2005;12(4):247-50. **Ineligible study design**
425. Janicak PG, Sharma RP, Pandey G, et al. Verapamil for the treatment of acute mania: a double-blind, placebo-controlled trial. *American Journal of Psychiatry*. 1998 Jul;155(7):972-3. PMID: 9659868 **Not treating bipolar**
426. Jefferson JW. Lamotrigine in psychiatry: pharmacology and therapeutics. *Cns Spectrums*. 2005 Mar;10(3):224-32. PMID: 15744223 **Ineligible study design**
427. Jensen HV, Davidsen K, Toftegaard L, et al. Double-blind comparison of the side-effect profiles of dasily versus alternate-day dosing schedules in lithium maintenance treatment of manic-depressive disorder. *Journal of Affective Disorders*. 1996 1996;36(3-4):89-93. doi: <http://dx.doi.org/10.1016/0165-0327%2895%2900052-6>. **No eligible outcomes reported**
428. Jensen HV, Holm J, Davidsen K, et al. Urinary excretion of albumin and transferrin in lithium maintenance treatment: daily versus alternate-day lithium dosing schedule. *Psychopharmacology*. 1995 Dec;122(3):317-20. PMID: 8748403 **No eligible outcomes reported**
429. Jensen HV, Plenge P, Mellerup ET, et al. Lithium prophylaxis of manic-depressive disorder: daily lithium dosing schedule versus every second day. *Acta Psychiatrica Scandinavica*. 1995 Jul;92(1):69-74. PMID: 7572251 **Bipolar not analyzed separately**
430. Jeste DV, Dolder CR. Treatment of non-schizophrenic disorders: Focus on atypical antipsychotics. *Journal of Psychiatric Research*. 2004 2004;38(1):73-103. doi: <http://dx.doi.org/10.1016/S0022-3956%2803%2900094-3>. **Ineligible study design**
431. Jeste DV, Dolder CR, Nayak GV, et al. Atypical antipsychotics in elderly patients with dementia or schizophrenia: Review of recent literature. *Harvard Review of Psychiatry*. 2005 2005;13(6):340-51. doi: <http://dx.doi.org/10.1080/10673220500433247>. **Ineligible study design**
432. Jiang Y, McCombs JS, Park SH. A Retrospective Cohort Study of Acute Kidney Injury Risk Associated with Antipsychotics. *CNS Drugs*. 2017 01 Apr;31(4):319-26. doi: <http://dx.doi.org/10.1007/s40263-017-0421-4>. PMID: 614799558 **Bipolar not analyzed separately**
433. Jindal RD, Thase ME. Integrating psychotherapy and pharmacotherapy to improve outcomes among patients with mood disorders. *Psychiatric Services*. 2003 Nov;54(11):1484-90. PMID: 14600307 **Ineligible study design**
434. Joas E, Karanti A, Song J, et al. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *British Journal of Psychiatry*. 2017 March;210(3):197-202. doi: <http://dx.doi.org/10.1192/bjp.bp.116.187989>. **No eligible outcomes reported**
435. Joffe RT. The use of thyroid supplements to augment antidepressant medication. *Journal of Clinical Psychiatry*. 1998;59 Suppl 5:26-9; discussion 30-1. PMID: 9635545 **Ineligible study design**
436. Johnson SL, Fulford D. Preventing mania: a preliminary examination of the GOALS Program. *Behavior Therapy*. 2009 Jun;40(2):103-13. doi: <http://dx.doi.org/10.1016/j.beth.2008.03.002>. PMID: 19433142 **Ineligible study design**

437. Jones RM, Thompson C, Bitter I. A systematic review of the efficacy and safety of second generation antipsychotics in the treatment of mania. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2006 Jan;21(1):1-9. PMID: 16487905 **Ineligible study design**
438. Jones S. Psychotherapy of bipolar disorder: A review. *Journal of Affective Disorders*. 2004 2004;80(2-3):101-14. doi: <http://dx.doi.org/10.1016/S0165-0327%2803%2900111-3>. **Ineligible study design**
439. Jones S, McGrath E, Hampshire K, et al. A randomised controlled trial of time limited CBT informed psychological therapy for anxiety in bipolar disorder. *BMC Psychiatry*. 2013;13:54. doi: <http://dx.doi.org/10.1186/1471-244X-13-54>. PMID: 23414176 **Not treating bipolar**
440. Jones S, Mulligan LD, Law H, et al. A randomised controlled trial of recovery focused CBT for individuals with early bipolar disorder. *BMC Psychiatry*. 2012;12:204. doi: <http://dx.doi.org/10.1186/1471-244X-12-204>. PMID: 23171304 **Ineligible study design**
441. Jones SH, Smith G, Mulligan LD, et al. Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: Randomized controlled pilot trial. *British Journal of Psychiatry*. 2015 01 Jan;206(1):58-66. doi: <http://dx.doi.org/10.1192/bjp.bp.113.141259>. PMID: 601137212 **Duplicate reference**
442. Juruena MF, Ottoni GL, Machado-Vieira R, et al. Bipolar I and II disorder residual symptoms: oxcarbazepine and carbamazepine as add-on treatment to lithium in a double-blind, randomized trial. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2009 Feb 1;33(1):94-9. doi: <http://dx.doi.org/10.1016/j.pnpbp.2008.10.012>. PMID: 19007842 **Ineligible study design**
443. Justo LP, Soares BG, Calil HM. Family interventions for bipolar disorder. *Cochrane Database of Systematic Reviews*. 2007(4):CD005167. PMID: 17943843 **Ineligible study design**
444. Kakkar AK, Rehan HS, Unni KE, et al. Comparative efficacy and safety of oxcarbazepine versus divalproex sodium in the treatment of acute mania: a pilot study. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2009 Apr;24(3):178-82. doi: <http://dx.doi.org/10.1016/j.eurpsy.2008.12.014>. PMID: 19324530 **Over 50% dropout rate**
445. Kantrowitz JT, Halberstam B, Gangwisch J. Single-dose ketamine followed by daily D-cycloserine in treatment-resistant bipolar depression. *Journal of Clinical Psychiatry*. 2015 Jun;76(6):737-8. doi: <http://dx.doi.org/10.4088/JCP.14109527>. PMID: 2015-34824-030 **Ineligible study design**
446. Kapsan A, Yaroslavsky Y, Applebaum J, et al. Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disorders*. 2003 Feb;5(1):36-9. PMID: 12656936 **Bipolar not analyzed separately**
447. Kasper S, Calabrese JR, Johnson G, et al. International consensus group on the evidence-based pharmacologic treatment of bipolar I and II depression. *Journal of Clinical Psychiatry*. 2008 2008;69(10):1632-46. doi: <http://dx.doi.org/10.4088/JCP.v69n1014>. **Ineligible study design**
448. Katagiri H, Takita Y, Tohen M, et al. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. *Current Medical Research & Opinion*. 2012 May;28(5):701-13. doi: <http://dx.doi.org/10.1185/03007995.2012.666961>. PMID: 22356118 **Over 50% dropout rate**
449. Katagiri H, Tohen M, McDonnell DP, et al. Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Japanese subpopulation analysis of a randomized, double-blind, placebo-controlled

study. BMC Psychiatry. 2013;13:138. doi: <http://dx.doi.org/10.1186/1471-244X-13-138>. PMID: 23672672

Ineligible study design

- 450. Katz MM, Maas JW, Frazer A, et al. Drug-induced actions on brain neurotransmitter systems and changes in the behaviors and emotions of depressed patients. Neuropsychopharmacology. 1994 Oct;11(2):89-100. PMID: 7530963 **Ineligible study design**
- 451. Keck PE, Jr. Long-term therapy of bipolar illness. Journal of Family Practice. 2003 Mar;Suppl:S18-21. PMID: 12676080 **Ineligible study design**
- 452. Keck PE, Jr. Defining and improving response to treatment in patients with bipolar disorder. Journal of Clinical Psychiatry. 2004;65 Suppl 15:25-9. PMID: 15554793 **Ineligible study design**
- 453. Keck PE, Jr. Bipolar depression: A new role for atypical antipsychotics? [References]. Bipolar Disorders. 2005;7(Suppl4):34-40. doi: <http://dx.doi.org/10.1111/j.1399-5618.2005.00213.x>. **Ineligible study design**
- 454. Keck PE, Jr., Bowden CL, Meinhold JM, et al. Relationship between serum valproate and lithium levels and efficacy and tolerability in bipolar maintenance therapy. International Journal of Psychiatry in Clinical Practice. 2005 2005;9(4):271-7. doi: <http://dx.doi.org/10.1080/13651500500305622>. PMID: 24930925 **Duplicate reference**
- 455. Keck PE, Jr., Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. Journal of Clinical Psychiatry. 2007 Oct;68(10):1480-91. PMID: 17960961 **Over 50% dropout rate**
- 456. Keck PE, Jr., Corya SA, Altshuler LL, et al. Analyses of treatment-emergent mania with olanzapine/fluoxetine combination in the treatment of bipolar depression. Journal of Clinical Psychiatry. 2005 May;66(5):611-6. PMID: 15889948 **Ineligible study design**
- 457. Keck PE, Jr., Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. American Journal of Psychiatry. 2003 Sep;160(9):1651-8. PMID: 12944341 **Over 50% dropout rate**
- 458. Keck PE, Jr., McElroy SL. Outcome in the pharmacologic treatment of bipolar disorder. Journal of Clinical Psychopharmacology. 1996 Apr;16(2 Suppl 1):15S-23S. PMID: 8707996 **Ineligible study design**
- 459. Keck PE, Jr., McElroy SL. Carbamazepine and valproate in the maintenance treatment of bipolar disorder. Journal of Clinical Psychiatry. 2002;63 Suppl 10:13-7. PMID: 12392348 **Ineligible study design**
- 460. Keck PE, Jr., McElroy SL. Divalproex in the treatment of bipolar disorder. Psychopharmacology Bulletin. 2003;37 Suppl 2:67-73. PMID: 15021862 **Ineligible study design**
- 461. Keck PE, Jr., McElroy SL. New approaches in managing bipolar depression. Journal of Clinical Psychiatry. 2003;64 Suppl 1:13-8. PMID: 12625800 **Ineligible study design**
- 462. Keck PE, Jr., McElroy SL, Strakowski SM. Anticonvulsants and antipsychotics in the treatment of bipolar disorder. Journal of Clinical Psychiatry. 1998;59 Suppl 6:74-81; discussion 2. PMID: 9674940 **Ineligible study design**

463. Keck PE, Jr., McElroy SL, Strakowski SM, et al. Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. *Journal of Clinical Psychiatry*. 2000;61 Suppl 4:33-8. PMID: 10739329
Ineligible study design
464. Keck PE, Jr., Mendlewicz J, Calabrese JR, et al. A review of randomized, controlled clinical trials in acute mania. *Journal of Affective Disorders*. 2000 Sep;59 Suppl 1:S31-S7. PMID: 11121825 **Ineligible study design**
465. Keck PE, Jr., Nelson EB, McElroy SL. Advances in the pharmacologic treatment of bipolar depression. *Biological Psychiatry*. 2003 Apr 15;53(8):671-9. PMID: 12706953 **Ineligible study design**
466. Keck PE, Orsulak PJ, Cutler AJ, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. *Journal of Affective Disorders*. 2009 Jan;112(1-3):36-49. doi: <http://dx.doi.org/10.1016/j.jad.2008.05.014>. PMID: 18835043 **Over 50% dropout rate**
467. Keck PE, Jr., Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *Journal of Clinical Psychiatry*. 2006;67 Suppl 1:8-15. PMID: 16426111 **Ineligible study design**
468. Keck PE, Jr., Versiani M, Warrington L, et al. Long-term safety and efficacy of ziprasidone in subpopulations of patients with bipolar mania. *Journal of Clinical Psychiatry*. 2009 Jun;70(6):844-51. PMID: 19573482 **No eligible outcomes reported**
469. Kelly T, Lieberman DZ. The Utility of Low-Dose Aripiprazole for the Treatment of Bipolar II and Bipolar NOS Depression. *Journal of Clinical Psychopharmacology*. 2017 01 Feb;37(1):99-101. doi: <http://dx.doi.org/10.1097/JCP.0000000000000636>. PMID: 613690731 **No eligible outcomes reported**
470. Kemp DE, Calabrese JR, Eudicone JM, et al. Predictive value of early improvement in bipolar depression trials: a post-hoc pooled analysis of two 8-week aripiprazole studies. *Psychopharmacology Bulletin*. 2010;43(2):5-27. PMID: 21052040 **Ineligible study design**
471. Kemp DE, Muzina DJ, McIntyre RS, et al. Bipolar depression: trial-based insights to guide patient care. *Dialogues in Clinical Neuroscience*. 2008;10(2):181-92. PMID: 18689288 **Ineligible study design**
472. Kemp DE, Sylvia LG, Calabrese JR, et al. General medical burden in bipolar disorder: Findings from the LiTMUS comparative effectiveness trial. *Acta Psychiatrica Scandinavica*. 2014 2014;129(1):24-34. doi: <http://dx.doi.org/10.1111/acps.12101>. **Ineligible study design**
473. Kessing LV, Gerds TA, Feldt-Rasmussen B, et al. Use of lithium and anticonvulsants and the rate of chronic kidney disease a nationwide population-based study. *JAMA Psychiatry*. 2015 December;72(12):1182-91. doi: <http://dx.doi.org/10.1001/jamapsychiatry.2015.1834>. PMID: 607152515
Ineligible study design
474. Kessing LV, Hansen HV, Christensen EM, et al. The effects of centralised and specialised combined pharmacological and psychological intervention compared with decentralised and non-specialised treatment in the early course of severe unipolar and bipolar affective disorders--design of two randomised clinical trials. *Trials [Electronic Resource]*. 2011;12(1):32. doi: <http://dx.doi.org/10.1186/1745-6215-12-32>. PMID: 21291564 **Ineligible study design**

475. Kessing LV, Hansen HV, Christensen EM, et al. Do young adults with bipolar disorder benefit from early intervention? *Journal of Affective Disorders*. 2014 Jan;152-154:403-8. doi: <http://dx.doi.org/10.1016/j.jad.2013.10.001>. PMID: 24268595 **No eligible outcomes reported**
476. Kessler U, Vaaler AE, Schoyen H, et al. The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. *BMC Psychiatry*. 2010;10:16. doi: <http://dx.doi.org/10.1186/1471-244X-10-16>. PMID: 20178636 **Ineligible study design**
477. Ketter TA, Amchin J, Frye MA, et al. Long-term safety and efficacy of armodafinil in bipolar depression: A 6-month open-label extension study. *Journal of Affective Disorders*. 2016 01 Jun;197:51-7. doi: <http://dx.doi.org/10.1016/j.jad.2016.02.050>. PMID: 608872019 **No eligible outcomes reported**
478. Ketter TA, Brooks JO, 3rd, Hoblyn JC, et al. Long-term effectiveness of quetiapine in bipolar disorder in a clinical setting. *Journal of Psychiatric Research*. 2010 Oct;44(14):921-9. doi: <http://dx.doi.org/10.1016/j.jpsychires.2010.02.005>. PMID: 20378127 **No eligible outcomes reported**
479. Ketter TA, Greist JH, Graham JA, et al. The effect of dermatologic precautions on the incidence of rash with addition of lamotrigine in the treatment of bipolar I disorder: a randomized trial. *Journal of Clinical Psychiatry*. 2006 Mar;67(3):400-6. PMID: 16649826 **Not bipolar disorder**
480. Ketter TA, Houston JP, Adams DH, et al. Differential efficacy of olanzapine and lithium in preventing manic or mixed recurrence in patients with bipolar I disorder based on number of previous manic or mixed episodes. *Journal of Clinical Psychiatry*. 2006 Jan;67(1):95-101. PMID: 16426094 **Over 50% dropout rate**
481. Ketter TA, Jenkins JB, Schroeder DH, et al. Carbamazepine but not valproate induces bupropion metabolism. *Journal of Clinical Psychopharmacology*. 1995 Oct;15(5):327-33. PMID: 8830063 **Ineligible study design**
482. Ketter TA, Jones M, Paulsson B. Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania. *Journal of Affective Disorders*. 2007;100 Suppl 1:S45-53. PMID: 17383011 **Duplicate reference**
483. Ketter TA, Post RM, Parekh PI, et al. Addition of monoamine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment-resistant depression. *Journal of Clinical Psychiatry*. 1995 Oct;56(10):471-5. PMID: 7559374 **Ineligible study design**
484. Ketter TA, Sarma K, Silva R, et al. LURASIDONE in the LONG-TERM TREATMENT of PATIENTS with BIPOLAR DISORDER: A 24-WEEK OPEN-LABEL EXTENSION STUDY. *Depression and Anxiety*. 2016 01 May;33(5):424-34. doi: <http://dx.doi.org/10.1002/da.22479>. PMID: 608756629 **No eligible outcomes reported**
485. Ketter TA, Wang PW, Chandler RA, et al. Dermatology precautions and slower titration yield low incidence of lamotrigine treatment-emergent rash. *Journal of Clinical Psychiatry*. 2005 May;66(5):642-5. PMID: 15889953 **Ineligible study design**

486. Ketter TA, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar i disorder. *Journal of Affective Disorders*. 2015 01 Aug;181:87-91. doi: <http://dx.doi.org/10.1016/j.jad.2015.04.012>. PMID: 2015012361 **Ineligible study design**
487. Khan A, Ginsberg LD, Asnis GM, et al. Effect of lamotrigine on cognitive complaints in patients with bipolar I disorder. *Journal of Clinical Psychiatry*. 2004 Nov;65(11):1483-90. PMID: 15554760 **Duplicate reference**
488. Kikkawa A, Kitamura Y, Aiba T, et al. Correlation between the efficacy of lamotrigine and the serum lamotrigine level during the remission phase of acute bipolar II depression: A naturalistic and unblinded prospective pilot study. *Biological and Pharmaceutical Bulletin*. 2017;40(4):413-8. doi: <http://dx.doi.org/10.1248/bpb.b16-00725>. PMID: 615121800 **Ineligible study design**
489. Kilbourne AM, Goodrich DE, Lai Z, et al. Randomized controlled trial to assess reduction of cardiovascular disease risk in patients with bipolar disorder: the Self-Management Addressing Heart Risk Trial (SMAHRT). *Journal of Clinical Psychiatry*. 2013 Jul;74(7):e655-62. doi: <http://dx.doi.org/10.4088/JCP.12m08082>. PMID: 23945460 **Ineligible intervention**
490. Kleindienst N, Greil W. Inter-episodic morbidity and drop-out under carbamazepine and lithium in the maintenance treatment of bipolar disorder. *Psychological Medicine*. 2002 Apr;32(3):493-501. PMID: 11989994 **Over 20% schizoaffective**
491. Kleindienst N, Greil W. Are illness concepts a powerful predictor of adherence to prophylactic treatment in bipolar disorder? *Journal of Clinical Psychiatry*. 2004 Jul;65(7):966-74. PMID: 15291686 **Ineligible study design**
492. Kleindienst N, Severus WE, Greil W. Are serum lithium levels related to the polarity of recurrence in bipolar disorders? Evidence from a multicenter trial. *International Clinical Psychopharmacology*. 2007 May;22(3):125-31. PMID: 17414737 **Ineligible study design**
493. Kluwe-Schiavon B, Viola TW, Levandowski ML, et al. A systematic review of cognitive rehabilitation for bipolar disorder. *Trends in Psychiatry and Psychotherapy*. 2015 October;37(4):194-201. doi: <http://dx.doi.org/10.1590/2237-6089-2015-0006>. PMID: 607358592 **Ineligible study design**
494. Kohler-Forsberg O, Sylvia L, Thase M, et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol do not affect 6-month mood-stabilizing treatment outcome among 482 patients with bipolar disorder. *Depression and Anxiety*. 2017 01 Mar;34(3):281-90. doi: <http://dx.doi.org/10.1002/da.22601>. PMID: 614328413 **Ineligible intervention**
495. Konovalov S, Muralee S, Tampi RR. Anticonvulsants for the treatment of behavioral and psychological symptoms of dementia: A literature review. *International Psychogeriatrics*. 2008 2008;20(2):293-308. doi: <http://dx.doi.org/10.1017/S1041610207006540>. **Ineligible study design**
496. Koukopoulos A, De Chiara L, Koukopoulos AE, et al. Three-year, naturalistic, mirror-image assessment of adding memantine to the treatment of 30 treatment-resistant patients with bipolar disorder. *The Journal of clinical psychiatry*. 2015 01 Jan;76(1):e91-e7. doi: <http://dx.doi.org/10.4088/JCP.13m08956>. PMID: 25650685 **No eligible outcomes reported**
497. Kramlinger KG, Phillips KA, Post RM. Rash complicating carbamazepine treatment. *Journal of Clinical Psychopharmacology*. 1994 Dec;14(6):408-13. PMID: 7884021 **Not treating bipolar**

498. Kruger S, Trevor Young L, Braunig P. Pharmacotherapy of bipolar mixed states. *Bipolar Disorders*. 2005 Jun;7(3):205-15. PMID: 15898959 **Ineligible study design**
499. Kulkarni J, Berk M, Wang W, et al. A four week randomised control trial of adjunctive medroxyprogesterone and tamoxifen in women with mania. *Psychoneuroendocrinology*. 2014 May;43:52-61. doi: <http://dx.doi.org/10.1016/j.psyneuen.2014.02.004>. PMID: 24703170 **Over 20% schizoaffective**
500. Kulkarni J, Garland KA, Scaffidi A, et al. A pilot study of hormone modulation as a new treatment for mania in women with bipolar affective disorder. *Psychoneuroendocrinology*. 2006 May;31(4):543-7. PMID: 16356651 **Less than 11 subjects per arm**
501. Kusalic M, Engelsmann F. Renal reactions to changes of lithium dosage. *Neuropsychobiology*. 1996;34(3):113-6. PMID: 8916067 **No eligible outcomes reported**
502. Kusumakar V, Yatham LN, Haslam DR, et al. Treatment of mania, mixed state, and rapid cycling. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 1997 Aug;42 Suppl 2:79S-86S. PMID: 9288440 **Ineligible study design**
503. Ladea M, Sinca MC, Barbu CM, et al. Clinical and therapeutical aspects of bipolar disorder: The switch on depakine chrono from other valproate treatments - Retrospective data collection. *Farmacia*. 2015 06 Aug;63(3):446-52. PMID: 605514200 **No eligible outcomes reported**
504. Lahera G, Benito A, Montes JM, et al. Social cognition and interaction training (SCIT) for outpatients with bipolar disorder. *Journal of Affective Disorders*. 2013 Mar 20;146(1):132-6. doi: <http://dx.doi.org/10.1016/j.jad.2012.06.032>. PMID: 22840617 **Ineligible study design**
505. Lam DH, Burbeck R, Wright K, et al. Psychological therapies in bipolar disorder: the effect of illness history on relapse prevention - a systematic review. *Bipolar Disorders*. 2009 Aug;11(5):474-82. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00724.x>. PMID: 19624386 **Ineligible study design**
506. Lam DH, McCrone P, Wright K, et al. Cost-effectiveness of relapse-prevention cognitive therapy for bipolar disorder: 30-month study. *British Journal of Psychiatry*. 2005 Jun;186:500-6. PMID: 15928361 **Ineligible intervention**
507. Landin-Romero R, Novo P, Vicens V, et al. EMDR therapy modulates the default mode network in a subsyndromal, traumatized bipolar patient. *Neuropsychobiology*. 2013;67(3):181-4. doi: <http://dx.doi.org/10.1159/000346654>. PMID: 23548794 **Ineligible study design**
508. Lao KSJ, He Y, Wong ICK, et al. Tolerability and Safety Profile of Cariprazine in Treating Psychotic Disorders, Bipolar Disorder and Major Depressive Disorder: A Systematic Review with Meta-Analysis of Randomized Controlled Trials. *CNS Drugs*. 2016 01 Nov;30(11):1043-54. doi: <http://dx.doi.org/10.1007/s40263-016-0382-z>. PMID: 611873767 **Ineligible study design**
509. Larsen ER, Saric K. Pregnancy and bipolar disorder: the risk of recurrence when discontinuing treatment with mood stabilisers: a systematic review. *Acta Neuropsychiatrica*. 2016 17 Nov:1-8. doi: <http://dx.doi.org/10.1017/neu.2016.60>. PMID: 613273686 **Ineligible study design**
510. Latalova K. Insight in bipolar disorder. *Psychiatric Quarterly*. 2012 Sep;83(3):293-310. doi: <http://dx.doi.org/10.1007/s11126-011-9200-4>. PMID: 22101737 **Ineligible study design**

511. Lauder S, Chester A, Castle D, et al. A randomized head to head trial of MoodSwings.net.au: an Internet based self-help program for bipolar disorder. *Journal of Affective Disorders*. 2015 Jan 15;171:13-21. doi: <http://dx.doi.org/10.1016/j.jad.2014.08.008>. PMID: 25282145 **Over 50% dropout rate**
512. Leadbetter R, Messenheimer J, Bentley B, et al. Mood-stabilizing properties of lamotrigine: A review of data from controlled clinical trials. *Psychiatric Annals*. 2002 2002;32(12):766-72. **Ineligible study design**
513. Lee AA, Laurent SM, Wykes TL, et al. Genetic attributions and mental illness diagnosis: effects on perceptions of danger, social distance, and real helping decisions. *Social Psychiatry & Psychiatric Epidemiology*. 2014 May;49(5):781-9. doi: <http://dx.doi.org/10.1007/s00127-013-0764-1>. PMID: 24068437 **Ineligible study design**
514. Lee JY, Harvey AG. Memory for therapy in bipolar disorder and Comorbid insomnia. *Journal of Consulting and Clinical Psychology*. 2015;83(1):92-102. doi: <http://dx.doi.org/10.1037/a0037911>. PMID: 2015868969 **Ineligible study design**
515. Leibenluft E, Turner EH, Feldman-Naim S, et al. Light therapy in patients with rapid cycling bipolar disorder: preliminary results. *Psychopharmacology Bulletin*. 1995;31(4):705-10. PMID: 8851643 **Less than 11 subjects per arm**
516. Lemoine P, Fondarai J, Faivre T. Valpromide increases amplitude of heart rate circadian rhythm in remitted bipolar and unipolar disorders. A placebo-controlled study. *European Psychiatry*. 2000 2000;15(7):424-32. doi: <http://dx.doi.org/10.1016/S0924-9338%2800%2900513-7>. PMID: 11112935 **No eligible outcomes reported**
517. Lepkifker E, Iancu I, Horesh N, et al. Lithium therapy for unipolar and bipolar depression among the middle-aged and older adult patient subpopulation. *Depression & Anxiety*. 2007;24(8):571-6. PMID: 17133442 **No eligible outcomes reported**
518. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *American Journal of Psychiatry*. 2006 Feb;163(2):232-9. PMID: 16449476 **No eligible outcomes reported**
519. Levin JB, Sams J, Tatsuoka C, et al. Use of automated medication adherence monitoring in bipolar disorder research: pitfalls, pragmatics, and possibilities. *Therapeutic Advances in Psychopharmacology*. 2015 02 Apr;5(2):76-87. doi: <http://dx.doi.org/10.1177/2045125314566807>. PMID: 2015886937 **Ineligible study design**
520. Levin JB, Tatsuoka C, Cassidy KA, et al. Trajectories of medication attitudes and adherence behavior change in non-adherent bipolar patients. *Comprehensive Psychiatry*. 2015 Apr;58:29-36. doi: <http://dx.doi.org/10.1016/j.comppsy.2014.11.023>. PMID: 25617964 **Ineligible study design**
521. Levine J, Barak Y, Kofman O, et al. Follow-up and relapse analysis of an inositol study of depression. *Israel Journal of Psychiatry & Related Sciences*. 1995;32(1):14-21. PMID: 7622343 **Bipolar not analyzed separately**

522. Levine J, Shectman T, Lefkifker E, et al. Inositol may reverse lithium-induced polydipsia but not polyuria. *Human Psychopharmacology: Clinical and Experimental*. 1997 1997;12(5):459-65. doi: [http://dx.doi.org/10.1002/%28SICI%291099-1077%28199709/10%2912:5%3C459::AID-HUP889%3E3.0.CO;2-K](http://dx.doi.org/10.1002/%28SICI%291099-1077%28199709%10%2912:5%3C459::AID-HUP889%3E3.0.CO;2-K). **No eligible outcomes reported**
523. Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. *Bipolar Disorders*. 2000 Jun;2(2):108-19. PMID: 11252650 **Ineligible study design**
524. Li DJ, Tseng PT, Chen YW, et al. Significant treatment effect of bupropion in patients with bipolar disorder but similar phase-shifting rate as other antidepressants: A meta-analysis following the PRISMA guidelines. *Medicine (United States)*. 2016;95(13):e3165. doi: <http://dx.doi.org/10.1097/MD.00000000000003165>. PMID: 609693558 **Ineligible study design**
525. Licht RW. Drug treatment of mania: a critical review. *Acta Psychiatrica Scandinavica*. 1998 Jun;97(6):387-97. PMID: 9669508 **Ineligible study design**
526. Licht RW, Gijsman H, Nolen WA, et al. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. *Acta Psychiatrica Scandinavica*. 2008 Nov;118(5):337-46. doi: <http://dx.doi.org/10.1111/j.1600-0447.2008.01237.x>. PMID: 18754834 **Ineligible study design**
527. Licht RW, Nielsen JN, Gram LF, et al. Lamotrigine versus lithium as maintenance treatment in bipolar I disorder: an open, randomized effectiveness study mimicking clinical practice. The 6th trial of the Danish University Antidepressant Group (DUAG-6). *Bipolar Disorders*. 2010 Aug;12(5):483-93. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00836.x>. PMID: 20712749 **Over 50% dropout rate**
528. Licht RW, Vestergaard P, Brodersen A. Long-term outcome of patients with bipolar disorder commenced on lithium prophylaxis during hospitalization: a complete 15-year register-based follow-up. *Bipolar Disorders*. 2008 Feb;10(1):79-86. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00499.x>. PMID: 18199244 **No eligible outcomes reported**
529. Licht RW, Vestergaard P, Kessing LV, et al. Psychopharmacological treatment with lithium and antiepileptic drugs: suggested guidelines from the Danish Psychiatric Association and the Child and Adolescent Psychiatric Association in Denmark. *Acta Psychiatrica Scandinavica, Supplementum*. 2003(419):1-22. PMID: 12974784 **Ineligible study design**
530. Lipkovich I, Citrome L, Perlis R, et al. Early predictors of substantial weight gain in bipolar patients treated with olanzapine. *Journal of Clinical Psychopharmacology*. 2006 Jun;26(3):316-20. PMID: 16702898 **Ineligible study design**
531. Lipkovich IA, Houston JP, Ahl J. Identifying patterns in treatment response profiles in acute bipolar mania: a cluster analysis approach. *BMC Psychiatry*. 2008;8:65. doi: <http://dx.doi.org/10.1186/1471-244X-8-65>. PMID: 18664256 **Ineligible study design**
532. Lobban F, Taylor L, Chandler C, et al. Enhanced relapse prevention for bipolar disorder by community mental health teams: cluster feasibility randomised trial. *British Journal of Psychiatry*. 2010 Jan;196(1):59-63. doi: <http://dx.doi.org/10.1192/bjp.bp.109.065524>. PMID: 20044662 **Ineligible study design**
533. Loebel A, Siu C, Pikalov A, et al. Remission in lurasidone-treated patients with bipolar i depression: Post-hoc analysis of a 6-week, placebo-controlled trial followed by a 6-month extension. *European Psychiatry*. 2015 31 Mar;30:1148. PMID: 71930816 **Ineligible study design**

534. Loebel A, Siu C, Rajagopalan K, et al. Recovery in bipolar depression: Post-hoc analysis of a placebo-controlled lurasidone trial followed by a long-term continuation study. *Journal of Affective Disorders*. 2015 17 Aug;186:376-82. doi: <http://dx.doi.org/10.1016/j.jad.2015.07.033>. PMID: 2015301525 **No eligible outcomes reported**
535. Lombardo I, Sachs G, Kolluri S, et al. Two 6-week, randomized, double, blind, placebo-controlled studies of ziparsidone in outpatients with bipolar I depression: Did baseline characteristics impact trial outcome? [References]. *Journal of Clinical Psychopharmacology*. 2012 2012;32(4):470-8. doi: <http://dx.doi.org/10.1097/JCP.0b013e31825ccde5>. **No eligible outcomes reported**
536. Loo CK, Sainsbury K, Sheehan P, et al. A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. *International Journal of Neuropsychopharmacology*. 2008 2008;11(7):883-90. doi: <http://dx.doi.org/10.1017/S1461145708009292>. **No eligible outcomes reported**
537. Lorberg B, Youssef NA, Bhagwagar Z. Lamotrigine-associated rash: To rechallenge or not to rechallenge? [References]. *International Journal of Neuropsychopharmacology*. 2009 2009;12(2):257-65. doi: <http://dx.doi.org/10.1017/S1461145708009504>. **Ineligible study design**
538. Lynch D, Laws KR, McKenna PJ. Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychological Medicine*. 2010 Jan;40(1):9-24. doi: <http://dx.doi.org/10.1017/S003329170900590X>. PMID: 19476688 **Ineligible study design**
539. Lyseng-Williamson KA, Perry CM. Aripiprazole: in acute mania associated with bipolar I disorder. *CNS Drugs*. 2004;18(6):367-76; discussion 77-8. PMID: 15089107 **Ineligible study design**
540. Machado-Vieira R. Purinergic system in the treatment of bipolar disorder: Uric acid levels as a screening test in mania. *Journal of Clinical Psychopharmacology*. 2012 2012;32(5):735-6. doi: <http://dx.doi.org/10.1097/JCP.0b013e318268391d>. **Ineligible study design**
541. Machado-Vieira R, Andreazza AC, Viale CI, et al. Oxidative stress parameters in unmedicated and treated bipolar subjects during initial manic episode: a possible role for lithium antioxidant effects. *Neuroscience Letters*. 2007 Jun 21;421(1):33-6. PMID: 17548157 **Ineligible study design**
542. Machado-Vieira R, Zarate CA, Jr. Proof of concept trials in bipolar disorder and major depressive disorder: a translational perspective in the search for improved treatments. *Depression & Anxiety*. 2011 Apr;28(4):267-81. doi: <http://dx.doi.org/10.1002/da.20800>. PMID: 21456037 **Ineligible study design**
543. Macritchie K, Geddes JR, Scott J, et al. Valproate for acute mood episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*. 2003(1):CD004052. PMID: 12535506 **Ineligible study design**
544. Macritchie KA, Geddes JR, Scott J, et al. Valproic acid, valproate and divalproex in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews*. 2001(3):CD003196. PMID: 11687047 **Ineligible study design**
545. Magalhaes PV, Dean OM, Bush AI, et al. N-acetylcysteine for major depressive episodes in bipolar disorder. *Revista Brasileira de Psiquiatria*. 2011 Dec;33(4):374-8. PMID: 22189927 **Ineligible intervention**

546. Magalhaes PV, Dean OM, Bush AI, et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. *Journal of Affective Disorders*. 2011 Mar;129(1-3):317-20. doi: <http://dx.doi.org/10.1016/j.jad.2010.08.001>. PMID: 20800897 **Ineligible intervention**
547. Magalhaes PV, Dean OM, Bush AI, et al. A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. *Australian & New Zealand Journal of Psychiatry*. 2013 Jun;47(6):564-8. doi: <http://dx.doi.org/10.1177/0004867413481631>. PMID: 23493756 **Ineligible intervention**
548. Maidment I. Update on the use of new anticonvulsants as mood stabilisers. *Psychiatric Bulletin*. 1999 1999;23(9):554-8. doi: <http://dx.doi.org/10.1192/pb.23.9.554>. **Ineligible study design**
549. Maidment ID. Gabapentin treatment for bipolar disorders. *Annals of Pharmacotherapy*. 2001 Oct;35(10):1264-9. PMID: 11675857 **Ineligible study design**
550. Maidment ID. The use of topiramate in mood stabilization. *Annals of Pharmacotherapy*. 2002 Jul-Aug;36(7-8):1277-81. PMID: 12086564 **Ineligible study design**
551. Maj M. Selection of the initial drug(s) in the treatment of bipolar disorder, depressed phase. *Modern Problems of Pharmacopsychiatry*. 1997;25:66-77. PMID: 9344370 **Ineligible study design**
552. Maj M. The impact of lithium prophylaxis on the course of bipolar disorder: a review of the research evidence. *Bipolar Disorders*. 2000 Jun;2(2):93-101. PMID: 11252656 **Ineligible study design**
553. Malhi GS, Adams D, Berk M. Is lithium in a class of its own? A brief profile of its clinical use. *Australian & New Zealand Journal of Psychiatry*. 2009 Dec;43(12):1096-104. doi: <http://dx.doi.org/10.3109/00048670903279937>. PMID: 20001408 **Ineligible study design**
554. Malhi GS, Adams D, Berk M. Medicating mood with maintenance in mind: bipolar depression pharmacotherapy. *Bipolar Disorders*. 2009 Jun;11 Suppl 2:55-76. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00711.x>. PMID: 19538686 **Ineligible study design**
555. Malhi GS, Bargh DM, Cashman E, et al. The clinical management of bipolar disorder complexity using a stratified model. *Bipolar Disorders*. 2012 May;14 Suppl 2:66-89. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.00993.x>. PMID: 22510037 **Ineligible study design**
556. Malhi GS, Berk M, Bourin M, et al. A typical mood stabilizers: a "typical role for atypical antipsychotics. *Acta Psychiatrica Scandinavica, Supplementum*. 2005(426):29-38. PMID: 16104066 **Ineligible study design**
557. Mallinger AG, Thase ME, Haskett R, et al. Verapamil augmentation of lithium treatment improves outcome in mania unresponsive to lithium alone: preliminary findings and a discussion of therapeutic mechanisms. *Bipolar Disorders*. 2008 Dec;10(8):856-66. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00636.x>. PMID: 19594501 **Fewer than 11 subjects per arm**
558. Marcus R. Aripiprazole improved time to any mood episode when added to mood stabilizer. *Psychiatric Annals*. 2011 2011;41(7):353. **Ineligible study design**

559. Martin DM, Chan H, Green MJ, et al. Transcranial direct current stimulation (tDCS) to remediate cognitive function in euthymic bipolar disorder patients. *Brain Stimulation*. 2015 March-April;8 (2):367-8. PMID: 71911914 **Ineligible study design**
560. Martinez JM, Marangell LB, Simon NM, et al. Baseline predictors of serious adverse events at one year among patients with bipolar disorder in STEP-BD. *Psychiatric Services*. 2005 Dec;56(12):1541-8. PMID: 16339616 **Ineligible study design**
561. Martinotti G, Andreoli S, Di Nicola M, et al. Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. *Human Psychopharmacology: Clinical and Experimental*. 2008 2008;23(5):417-24. doi: <http://dx.doi.org/10.1002/hup.944>. **Ineligible study design**
562. Martinotti G, Sepede G, Signorelli M, et al. Efficacy and safety of fluoxetine monotherapy in bipolar depression: a systematic review. *Expert Opinion on Pharmacotherapy*. 2013 Jun;14(8):1065-75. doi: <http://dx.doi.org/10.1517/14656566.2013.783014>. PMID: 23527943 **Ineligible study design**
563. Masand PS, Eudicone J, Pikalov A, et al. Criteria for defining symptomatic and sustained remission in bipolar I disorder: a post-hoc analysis of a 26-week aripiprazole study (study CN138-010). *Psychopharmacology Bulletin*. 2008;41(2):12-23. PMID: 18668014 **Over 50% dropout rate**
564. Mazza M, Di Nicola M, Martinotti G, et al. Oxcarbazepine in bipolar disorder: a critical review of the literature. *Expert Opinion on Pharmacotherapy*. 2007 Apr;8(5):649-56. PMID: 17376019 **Ineligible study design**
565. McCloud TL, Caddy C, Jochim J, et al. Ketamine and other glutamate receptor modulators for depression in bipolar disorder in adults. *The Cochrane database of systematic reviews*. 2015;9:CD011611. doi: <http://dx.doi.org/10.1002/14651858.CD011611.pub2>. PMID: 609677719 **Ineligible study design**
566. McClure D, Greenman SC, Koppolu SS, et al. A Pilot Study of Safety and Efficacy of Cranial Electrotherapy Stimulation in Treatment of Bipolar II Depression. *Journal of Nervous & Mental Disease*. 2015 Nov;203(11):827-35. doi: <http://dx.doi.org/10.1097/NMD.0000000000000378>. PMID: 26414234 **Less than 11 subjects per arm**
567. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar I disorder. *Drugs*. 2004;64(23):2709-26. PMID: 15537371 **Ineligible study design**
568. McDonell MG, Srebnik D, Angelo F, et al. Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness. *American Journal of Psychiatry*. 2013 Jan 1;170(1):94-101. PMID: 23138961 **Bipolar not analyzed separately**
569. McElroy SL, Keck PE, Jr. Pharmacologic agents for the treatment of acute bipolar mania. *Biological Psychiatry*. 2000 Sep 15;48(6):539-57. PMID: 11018226 **Ineligible study design**
570. McElroy SL, Martens BE, Creech RS, et al. Randomized, double-blind, placebo-controlled study of divalproex extended release loading monotherapy in ambulatory bipolar spectrum disorder patients with moderate-to-severe hypomania or mild mania. *Journal of Clinical Psychiatry*. 2010 May;71(5):557-65. doi: <http://dx.doi.org/10.4088/JCP.08m04854yel>. PMID: 20361901 **Over 50% dropout rate**

571. McElroy SL, Winstanley E, Mori N, et al. A randomized, placebo-controlled study of zonisamide to prevent olanzapine-associated weight gain. *Journal of Clinical Psychopharmacology*. 2012 Apr;32(2):165-72. doi: <http://dx.doi.org/10.1097/JCP.0b013e3182488758>. PMID: 22367654 **Not treating bipolar**
572. McElroy SL, Winstanley EL, Martens B, et al. A randomized, placebo-controlled study of adjunctive ramelteon in ambulatory bipolar I disorder with manic symptoms and sleep disturbance. *International Clinical Psychopharmacology*. 2011 Jan;26(1):48-53. doi: <http://dx.doi.org/10.1097/YIC.0b013e3283400d35>. PMID: 20861739 **Fewer than 11 subjects per arm**
573. McElroy SL, Zarate CA, Cookson J, et al. A 52-week, open-label continuation study of lamotrigine in the treatment of bipolar depression. *Journal of Clinical Psychiatry*. 2004 Feb;65(2):204-10. PMID: 15003074 **No eligible outcomes reported**
574. McFarlane WR, Dixon L, Lukens E, et al. Family psychoeducation and schizophrenia: A review of the literature. *Journal of Marital and Family Therapy*. 2003 2003;29(2):223-45. doi: <http://dx.doi.org/10.1111/j.1752-0606.2003.tb01202.x>. **Ineligible study design**
575. McGee V, Whittingham P. Society for Neuroscience--38th Annual Meeting--Therapeutic approaches for Alzheimer's disease, schizophrenia and bipolar disorder. *Idrugs*. 2009 Jan;12(1):14-6. PMID: 19127498 **Ineligible study design**
576. McGirr A, Vohringer PA, Ghaemi SN, et al. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry*. 2016 01 Dec;3(12):1138-46. doi: <http://dx.doi.org/10.1016/S2215-0366%2816%2930264-4>. PMID: 613441082 **Ineligible study design**
577. McIntyre R, Katzman M. The role of atypical antipsychotics in bipolar depression and anxiety disorders. *Bipolar Disorders*. 2003;5 Suppl 2:20-35. PMID: 14700010 **Ineligible study design**
578. McIntyre RS. Aripiprazole for the maintenance treatment of bipolar I disorder: A review. *Clinical Therapeutics*. 2010;32 Suppl 1:S32-8. doi: <http://dx.doi.org/10.1016/j.clinthera.2010.01.022>. PMID: 20152551 **Ineligible study design**
579. McIntyre RS, Cohen M, Zhao J, et al. Asenapine versus olanzapine in acute mania: a double-blind extension study.[Erratum appears in *Bipolar Disord*. 2010 Feb;12(1):112]. *Bipolar Disorders*. 2009 Dec;11(8):815-26. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00749.x>. PMID: 19832806 **No eligible outcomes reported**
580. McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010 Nov;126(3):358-65. doi: <http://dx.doi.org/10.1016/j.jad.2010.04.005>. PMID: 20537396 **Ineligible study design**
581. McIntyre RS, Konarski JZ, Jones M, et al. Quetiapine in the treatment of acute bipolar mania: efficacy across a broad range of symptoms. *Journal of Affective Disorders*. 2007;100 Suppl 1:S5-14. PMID: 17391773 **Duplicate reference**
582. McIntyre RS, Mancini DA, McCann S, et al. Valproate, bipolar disorder and polycystic ovarian syndrome. *Bipolar Disorders*. 2003 Feb;5(1):28-35. PMID: 12656935 **Ineligible study design**

583. McIntyre RS, Mancini DA, McCann S, et al. Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. *Bipolar Disorders*. 2002 Jun;4(3):207-13. PMID: 12180276 **Ineligible study design**
584. McIntyre RS, Soczynska JK, Lewis GF, et al. Managing psychiatric disorders with antidiabetic agents: translational research and treatment opportunities. *Expert Opinion on Pharmacotherapy*. 2006 Jul;7(10):1305-21. PMID: 16805717 **Ineligible study design**
585. McIntyre RS, Soczynska JK, Woldeyohannes HO, et al. Aripiprazole: pharmacology and evidence in bipolar disorder. *Expert Opinion on Pharmacotherapy*. 2007 May;8(7):1001-9. PMID: 17472545 **Ineligible study design**
586. McNamara B, Ray JL, Arthurs OJ, et al. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine*. 2001 2001;31(7):1141-6. doi: <http://dx.doi.org/10.1017/S0033291701004378>. **Ineligible study design**
587. Meador KJ. Newer anticonvulsants: dosing strategies and cognition in treating patients with mood disorders and epilepsy. *Journal of Clinical Psychiatry*. 2003;64 Suppl 8:30-4. PMID: 12892539 **Ineligible study design**
588. Mech AW. High-dose ziprasidone monotherapy in bipolar I disorder patients with depressed or mixed episodes. *Journal of Clinical Psychopharmacology*. 2008 2008;28(2):240-1. doi: <http://dx.doi.org/10.1097/JCP.0b013e31816745de>. **Ineligible study design**
589. Mei-Dan E, Ray JG, Vigod SN. Perinatal outcomes among women with bipolar disorder: a population-based cohort study. *American Journal of Obstetrics & Gynecology*. 2015 Mar;212(3):367.e1-8. doi: <http://dx.doi.org/10.1016/j.ajog.2014.10.020>. PMID: 25446660 **Ineligible intervention**
590. Meltzer HY. Focus on the metabolic consequences of long-term treatment with olanzapine, quetiapine and risperidone: Are there differences? [References]. *International Journal of Neuropsychopharmacology*. 2005 2005;8(2):153-6. doi: <http://dx.doi.org/10.1017/S1461145705005183>. **Ineligible study design**
591. Meltzer HY, Bonaccorso S, Bobo WV, et al. A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. *Journal of Clinical Psychiatry*. 2011 Dec;72(12):1602-10. doi: <http://dx.doi.org/10.4088/JCP.10m05997>. PMID: 21813074 **Bipolar not analyzed separately**
592. Meric G, Gracitelli GC, Gortz S, et al. Fresh osteochondral allograft transplantation for bipolar reciprocal osteochondral lesions of the knee. *American Journal of Sports Medicine*. 2015 Mar;43(3):709-14. doi: <http://dx.doi.org/10.1177/0363546514562549>. PMID: 25573390 **Not bipolar disorder**
593. Michalak EE, Guiraud-Diawara A, Sapin C. Asenapine treatment and health-related quality of life in patients experiencing bipolar I disorder with mixed episodes: post-hoc analyses of pivotal trials. *Current Medical Research & Opinion*. 2014 Apr;30(4):711-8. doi: <http://dx.doi.org/10.1185/03007995.2013.874988>. PMID: 24329543 **No eligible outcomes reported**
594. Miklowitz DJ. Adjunctive psychotherapy for bipolar disorder: state of the evidence. *American Journal of Psychiatry*. 2008 Nov;165(11):1408-19. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.08040488>. PMID: 18794208 **Ineligible study design**

595. Miklowitz DJ. Psychosocial interventions for bipolar disorder: A critical review of evidence for efficacy. Yatham, Lakshmi N [Ed]; Kusumakar, Vivek [Ed]. (2009). 2009 pp;Bipolar disorder:A clinician's guide to treatment management (2nd ed.). (pp. 575-90). xvi. **Ineligible study design**
596. Milano W, Grillo F, Del Mastro A, et al. Appropriate intervention strategies for weight gain induced by olanzapine: a randomized controlled study. *Advances in Therapy*. 2007 Jan-Feb;24(1):123-34. PMID: 17526469 **No eligible outcomes reported**
597. Millar A, Espie CA, Scott J. The sleep of remitted bipolar outpatients: a controlled naturalistic study using actigraphy. *Journal of Affective Disorders*. 2004 Jun;80(2-3):145-53. PMID: 15207927 **Not treating bipolar**
598. Miller IW, Uebelacker LA, Keitner GI, et al. Longitudinal course of bipolar I disorder. *Comprehensive Psychiatry*. 2004 Nov-Dec;45(6):431-40. PMID: 15526253 **Ineligible study design**
599. Minnai GP, Salis PG, Oppo R, et al. Effectiveness of maintenance electroconvulsive therapy in rapid-cycling bipolar disorder. *Journal of ECT*. 2011 Jun;27(2):123-6. doi: <http://dx.doi.org/10.1097/YCT.0b013e3181dbf797>. PMID: 20559148 **Less than 11 subjects per arm**
600. Mishory A, Winokur M, Bersudsky Y. Prophylactic effect of phenytoin in bipolar disorder: a controlled study. *Bipolar Disorders*. 2003 Dec;5(6):464-7. PMID: 14636372 **Over 50% dropout rate**
601. Mishory A, Yaroslavsky Y, Bersudsky Y, et al. Phenytoin as an antimanic anticonvulsant: a controlled study. *American Journal of Psychiatry*. 2000 Mar;157(3):463-5. PMID: 10698828 **Bipolar not analyzed separately**
602. Miskowiak KW, Vinberg M, Macoveanu J, et al. Effects of Erythropoietin on Hippocampal Volume and Memory in Mood Disorders. *Biological Psychiatry*. 2015 Aug 15;78(4):270-7. doi: <http://dx.doi.org/10.1016/j.biopsych.2014.12.013>. PMID: 25641635 **Bipolar not analyzed separately**
603. Mitchell PB, Malhi GS. The expanding pharmacopoeia for bipolar disorder. *Annual Review of Medicine*. 2002;53:173-88. PMID: 11818469 **Ineligible study design**
604. Mizziou S, Tsitsipa E, Moysidou S, et al. Psychosocial treatment and interventions for bipolar disorder: A systematic review. *Annals of General Psychiatry*. 2015;07doi: <http://dx.doi.org/10.1186/s12991-015-0057-z>. PMID: 605105502 **Ineligible study design**
605. Mohan TS, Tharyan P, Alexander J, et al. Effects of stimulus intensity on the efficacy and safety of twice-weekly, bilateral electroconvulsive therapy (ECT) combined with antipsychotics in acute mania: a randomised controlled trial. *Bipolar Disorders*. 2009 Mar;11(2):126-34. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00668.x>. PMID: 19267695 **Bipolar not analyzed separately**
606. Mokhber N, Lane CJ, Azarpazhooh MR, et al. Anticonvulsant treatments of dysphoric mania: A trial of gabapentin, lamotrigine and carbamazepine in Iran. *Neuropsychiatric Disease and Treatment*. 2008;4(1-B):227-34. **No eligible outcomes reported**

607. Moller HJ, Grunze H, Broich K. Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice? A conceptual review. *European Archives of Psychiatry & Clinical Neuroscience*. 2006 Feb;256(1):1-16. PMID: 16078087
Ineligible study design
608. Moncrieff J. Lithium revisited. A re-examination of the placebo-controlled trials of lithium prophylaxis in manic-depressive disorder. *British Journal of Psychiatry*. 1995 Nov;167(5):569-73; discussion 73-4. PMID: 8564310 **Ineligible study design**
609. Moore DJ, Poquette A, Casaletto KB, et al. Individualized Texting for Adherence Building (iTAB): Improving antiretroviral dose timing among HIV-infected persons with co-occurring bipolar disorder. *AIDS and Behavior*. 2015 Mar;19(3):459-71. doi: <http://dx.doi.org/10.1007/s10461-014-0971-0>. PMID: 2014-55785-001 **Not bipolar disorder**
610. Moreno RA, Hanna MM, Tavares SM, et al. A double-blind comparison of the effect of the antipsychotics haloperidol and olanzapine on sleep in mania. *Brazilian Journal of Medical & Biological Research*. 2007 Mar;40(3):357-66. PMID: 17334533 **Over 50% dropout rate**
611. Morriss RK, Faizal MA, Jones AP, et al. Interventions for helping people recognise early signs of recurrence in bipolar disorder. *Cochrane Database of Systematic Reviews*. 2007(1):CD004854. PMID: 17253526 **Ineligible study design**
612. Morriss RK, Lobban F, Jones S, et al. Pragmatic randomised controlled trial of group psychoeducation versus group support in the maintenance of bipolar disorder. *BMC Psychiatry*. 2011;11:114. doi: <http://dx.doi.org/10.1186/1471-244X-11-114>. PMID: 21777426 **Ineligible intervention**
613. Mueser KT, Pratt SI, Bartels SJ, et al. Randomized trial of social rehabilitation and integrated health care for older people with severe mental illness. *Journal of Consulting & Clinical Psychology*. 2010 Aug;78(4):561-73. doi: <http://dx.doi.org/10.1037/a0019629>. PMID: 20658812 **Bipolar not analyzed separately**
614. Muller-Oerlinghausen B, Retzow A, Henn FA, et al. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. European Valproate Mania Study Group. *Journal of Clinical Psychopharmacology*. 2000 Apr;20(2):195-203. PMID: 10770458 **Bipolar not analyzed separately**
615. Mundo E, Cattaneo E, Zanoni S, et al. The use of atypical antipsychotics beyond psychoses: Efficacy of quetiapine in bipolar disorder. *Neuropsychiatric Disease and Treatment*. 2006;2(2):139-48. doi: <http://dx.doi.org/10.2147/ndt.2006.2.2.139>. **Ineligible study design**
616. Muralidharan K, Ali M, Silveira LE, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: A meta-analysis of placebo-controlled trials. *Journal of Affective Disorders*. 2013 5, 2013;150(2):408-14. doi: <http://dx.doi.org/10.1016/j.jad.2013.04.032>. **Ineligible study design**
617. Murray G, Leitan ND, Berk M, et al. Online mindfulness-based intervention for late-stage bipolar disorder: pilot evidence for feasibility and effectiveness. *Journal of Affective Disorders*. 2015 Jun 1;178:46-51. doi: <http://dx.doi.org/10.1016/j.jad.2015.02.024>. PMID: 25795535 **Ineligible study design**

618. Muzina DJ, Calabrese JR. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. *Australian & New Zealand Journal of Psychiatry*. 2005 Aug;39(8):652-61. PMID: 16050919 **Ineligible study design**
619. Muzina DJ, Elhaj O, Gajwani P, et al. Lamotrigine and antiepileptic drugs as mood stabilizers in bipolar disorder. *Acta Psychiatrica Scandinavica, Supplementum*. 2005(426):21-8. PMID: 15833097 **Ineligible study design**
620. Muzina DJ, El-Sayegh S, Calabrese JR. Antiepileptic drugs in psychiatry-focus on randomized controlled trial. *Epilepsy Research*. 2002 Jun;50(1-2):195-202. PMID: 12151129 **Ineligible study design**
621. Muzina DJ, Momah C, Eudicone JM, et al. Aripiprazole monotherapy in patients with rapid-cycling bipolar I disorder: an analysis from a long-term, double-blind, placebo-controlled study. *International Journal of Clinical Practice*. 2008 May;62(5):679-87. doi: <http://dx.doi.org/10.1111/j.1742-1241.2008.01735.x>. PMID: 18373615 **Fewer than 11 subjects per arm**
622. Nahas Z, Kozel FA, Li X, et al. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disorders*. 2003 Feb;5(1):40-7. PMID: 12656937 **Ineligible study design**
623. Nahas Z, Teneback C, Chae JH, et al. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology*. 2007 Aug;32(8):1649-60. PMID: 17203016 **No eligible outcomes reported**
624. Nakamura K, Iga J, Matsumoto N, et al. Risk of bipolar disorder and psychotic features in patients initially hospitalised with severe depression. *Acta Neuropsychiatrica*. 2015 Apr;27(2):113-8. doi: <http://dx.doi.org/10.1017/neu.2014.42>. PMID: 25529988 **Not treating bipolar**
625. Narendran R, Young CM, Valenti AM, et al. Olanzapine therapy in treatment-resistant psychotic mood disorders: a long-term follow-up study. *Journal of Clinical Psychiatry*. 2001 Jul;62(7):509-16. PMID: 11488360 **Bipolar not analyzed separately**
626. Nasrallah HA, Brecher M, Paulsson B. Placebo-level incidence of extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. *Bipolar Disorders*. 2006 Oct;8(5 Pt 1):467-74. PMID: 17042884 **Duplicate reference**
627. Nejtek VA, Avila M, Chen LA, et al. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *Journal of Clinical Psychiatry*. 2008 Aug;69(8):1257-66. PMID: 18681757 **Over 50% dropout rate**
628. Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. *Journal of Clinical Psychiatry*. 2005;66 Suppl 8:13-21. PMID: 16336032 **Ineligible study design**
629. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of major depression. *The American Journal of Psychiatry*. 2001 2001;158(6):906-12. doi: <http://dx.doi.org/10.1176/appi.ajp.158.6.906>. **No eligible outcomes reported**
630. Nery FG, Monkul ES, Hatch JP, et al. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. *Human*

Psychopharmacology. 2008 Mar;23(2):87-94. doi: <http://dx.doi.org/10.1002/hup.912>. PMID: 18172906

No eligible outcomes reported

631. Newcomer JW, Tsai J, Pikalov A, et al. Effect of lurasidone on metabolic parameters in patients with bipolar depression. *European Psychiatry*. 2015 31 Mar;30:1140. PMID: 71931686 **Ineligible study design**
632. Ng F, Dodd S, Berk M. Atypical antipsychotics for bipolar disorder: Overblown or blown over? [References]. *Clinical Psychopharmacology and Neuroscience*. 2007 2007;5(2):53-64. **Ineligible study design**
633. Nguyen LN, Guthrie SK. Risperidone treatment of bipolar mania. *Annals of Pharmacotherapy*. 2006 Apr;40(4):674-82. PMID: 16569811 **Ineligible study design**
634. Niciu MJ, Xu AJ, Lundin NB, et al. Lithium and valproate levels do not correlate with ketamine's antidepressant efficacy in treatment-resistant bipolar depression. *Biological Psychiatry*. 2015 01 May;1):130S. PMID: 71846495 **Ineligible study design**
635. Niedermier JA, Nasrallah HA. Clinical correlates of response to valproate in geriatric inpatients. *Annals of Clinical Psychiatry*. 1998 Dec;10(4):165-8. PMID: 9988057 **Ineligible study design**
636. Nierenberg AA. An analysis of the efficacy of treatments for bipolar depression. *Journal of Clinical Psychiatry*. 2008;69 Suppl 5:4-8. PMID: 19265634 **Ineligible study design**
637. Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. *The American Journal of Psychiatry*. 1994 1994;151(7):1069-72. **Bipolar not analyzed separately**
638. Nierenberg AA, Alpert JE, Gardner-Schuster EE, et al. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. *Biological Psychiatry*. 2008 Sep 15;64(6):455-60. doi: <http://dx.doi.org/10.1016/j.biopsych.2008.04.036>. PMID: 18571625 **Less than 11 subjects per arm**
639. Nivoli AM, Murru A, Vieta E. Lithium: still a cornerstone in the long-term treatment in bipolar disorder? *Neuropsychobiology*. 2010;62(1):27-35. doi: <http://dx.doi.org/10.1159/000314307>. PMID: 20453532 **Ineligible study design**
640. No authorship i. 2nd Biennial Conference of the International Society for Bipolar Disorders: Edinburgh, Scotland, 2-4 August 2006. *Bipolar Disorders*. 2006 2006;8(Suppl 1):1. **Ineligible study design**
641. Nolen WA, Bloemkolk D. Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. *Neuropsychobiology*. 2000;42 Suppl 1:11-7. PMID: 11093064 **Ineligible study design**
642. Nolen WA, Kupka RW, Hellemann G, et al. Tranylcypromine vs. lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. *Acta Psychiatrica Scandinavica*. 2007 May;115(5):360-5. PMID: 17430413 **No eligible outcomes reported**
643. Nolen WA, Weisler RH. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). *Bipolar Disorders*. 2013

- Feb;15(1):100-9. doi: <http://dx.doi.org/10.1111/bdi.12027>. PMID: 23228201 **No eligible outcomes reported**
644. Novick D, Gonzalez-Pinto A, Haro JM, et al. Translation of randomised controlled trial findings into clinical practice: comparison of olanzapine and valproate in the EMBLEM study. *Pharmacopsychiatry*. 2009 Jul;42(4):145-52. doi: <http://dx.doi.org/10.1055/s-0028-1128115>. PMID: 19585393 **Ineligible study design**
645. Novick D, Reed C, Haro JM, et al. Comparison of olanzapine and risperidone in the EMBLEM Study: translation of randomized controlled trial findings into clinical practice. *International Clinical Psychopharmacology*. 2010 Sep;25(5):257-63. doi: <http://dx.doi.org/10.1097/YIC.0b013e32833b8fe4>. PMID: 20531011 **Over 50% dropout rate**
646. Obrocea GV, Dunn RM, Frye MA, et al. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biological Psychiatry*. 2002 2002;51(3):253-60. doi: <http://dx.doi.org/10.1016/S0006-3223%2801%2901206-9>. **Ineligible study design**
647. O'Donnell M, Parker G, Proberts M, et al. A study of client-focused case management and consumer advocacy: The Community and Consumer Service Project. *Australian and New Zealand Journal of Psychiatry*. 1999 1999;33(5):684-93. doi: <http://dx.doi.org/10.1046/j.1440-1614.1999.00629.x>. **Bipolar not analyzed separately**
648. Oertel-Knochel V, Reuter J, Reinke B, et al. Association between age of disease-onset, cognitive performance and cortical thickness in bipolar disorders. *Journal of Affective Disorders*. 2015 Mar 15;174:627-35. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.060>. PMID: 25577157 **Ineligible intervention**
649. O'Garro-Moore JK, Adams AM, Abramson LY, et al. Anxiety comorbidity in bipolar spectrum disorders: the mediational role of perfectionism in prospective depressive symptoms. *Journal of Affective Disorders*. 2015 Mar 15;174:180-7. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.024>. PMID: 25499686 **Ineligible intervention**
650. Ohtani T, Nishimura Y, Takahashi K, et al. Association between longitudinal changes in prefrontal hemodynamic responses and social adaptation in patients with bipolar disorder and major depressive disorder. *Journal of Affective Disorders*. 2015 May 1;176:78-86. doi: <http://dx.doi.org/10.1016/j.jad.2015.01.042>. PMID: 25702603 **Ineligible intervention**
651. O'Malley AJ, Zelevinsky K, He Y, et al. Do Patients at Sites With High RCT Enrollment Propensity Have Better Outcomes? *Medical Care*. 2015 Nov;53(11):989-95. doi: <http://dx.doi.org/10.1097/MLR.0000000000000429>. PMID: 26465127 **Not treating bipolar**
652. Ongur D, Lewandowski KE. Brain activation changes in psychotic disorders in response to targeted cognitive training. *Biological Psychiatry*. 2015 01 May;1):10S. PMID: 71846196 **Ineligible study design**
653. Oostervink F, Nolen WA, Kok RM, et al. Two years' outcome of acute mania in bipolar disorder: different effects of age and age of onset. *International Journal of Geriatric Psychiatry*. 2015 Feb;30(2):201-9. doi: <http://dx.doi.org/10.1002/gps.4128>. PMID: 24798245 **Ineligible intervention**

654. Oquendo MA, Galfalvy HC, Currier D, et al. Treatment of suicide attempters with bipolar disorder: a randomized clinical trial comparing lithium and valproate in the prevention of suicidal behavior.[Erratum appears in Am J Psychiatry. 2012 Feb;169(2):223]. American Journal of Psychiatry. 2011 Oct;168(10):1050-6. doi: <http://dx.doi.org/10.1176/appi.ajp.2011.11010163>. PMID: 21768611 **Over 50% dropout rate**
655. Oral TE. Treatment of acute mania. Neuroendocrinology Letters. 2005 Aug;26 Suppl 1:9-25. PMID: 16361986 **Ineligible study design**
656. Ostacher M, Ng-Mak D, Patel P, et al. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. World Journal of Biological Psychiatry. 2017 06 Mar;1-11. doi: <http://dx.doi.org/10.1080/15622975.2017.1285050>. PMID: 614711266 **Ineligible study design**
657. Ostacher MJ, Nierenberg AA, Rabideau D, et al. A clinical measure of suicidal ideation, suicidal behavior, and associated symptoms in bipolar disorder: Psychometric properties of the Concise Health Risk Tracking Self-Report (CHRT-SR). Journal of Psychiatric Research. 2015 Dec;71:126-33. doi: <http://dx.doi.org/10.1016/j.jpsychires.2015.10.004>. PMID: 26476489 **Ineligible study design**
658. Ostinelli EG, Cavallotti S, Castelnovo A, et al. Asenapine in the Treatment of Acute Mania: A Real-World Observational Study With 6 Months Follow-Up. Journal of Clinical Psychopharmacology. 2015 Oct;35(5):553-8. doi: <http://dx.doi.org/10.1097/JCP.0000000000000374>. PMID: 26252438 **Fewer than 11 subjects per arm**
659. Ouyang WC, Hsu MC, Yeh IN, et al. Efficacy and safety of combination of risperidone and haloperidol with divalproate in patients with acute mania. International Journal of Psychiatry in Clinical Practice. 2012 Sep;16(3):178-88. doi: <http://dx.doi.org/10.3109/13651501.2011.644564>. PMID: 22404731 **Over 20% schizoaffective**
660. Owen RT. Extended-release carbamazepine for acute bipolar mania: a review. Drugs of Today. 2006 May;42(5):283-9. PMID: 16801991 **Ineligible study design**
661. Owen RT. Olanzapine/fluoxetine combination for bipolar depression and other mood disorders: a review. Drugs of Today. 2006 Mar;42(3):185-92. PMID: 16628260 **Ineligible study design**
662. Pacchiarotti I, Valenti M, Colom F, et al. Differential outcome of bipolar patients receiving antidepressant monotherapy versus combination with an antimanic drug. Journal of Affective Disorders. 2011 Mar;129(1-3):321-6. doi: <http://dx.doi.org/10.1016/j.jad.2010.07.036>. PMID: 20817267 **Ineligible study design**
663. Pae CU, Kim TS, Kim JJ, et al. Long-term treatment of adjunctive quetiapine for bipolar mania. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2005 Jun;29(5):763-6. PMID: 15951090 **Ineligible study design**
664. Pae CU, Nassir Ghaemi S, Kim TS, et al. Rapid titration versus conventional titration of quetiapine in the treatment of bipolar mania: a preliminary trial. International Clinical Psychopharmacology. 2005 Nov;20(6):327-30. PMID: 16192842 **Ineligible study design**
665. Pae CU, Patkar AA, Gilmer W, et al. Predictors of response to ziprasidone: Results from a 6-week randomized double-blind, placebo-controlled trial for acute depressive mixed state. Pharmacopsychiatry. 2012 2012;45(4):152-5. doi: <http://dx.doi.org/10.1055/s-0031-1297984>. **Ineligible study design**

666. Pande AC, Crockatt JG, Janney CA, et al. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. *Bipolar Disorders*. 2000 Sep;2(3 Pt 2):249-55. PMID: 11249802 **Ineligible study design**
667. Pappadopulos E, Newcomer JW, Kolluri S. Changes in weight, plasma lipids, and glucose in adults treated with ziprasidone: a comprehensive analysis of pfizer-initiated clinical trials. *Journal of Clinical Psychiatry*. 2012 Jun;73(6):e742-8. doi: <http://dx.doi.org/10.4088/JCP.10r06802>. PMID: 22795213 **Not treating bipolar**
668. Parikh SV, Hawke LD, Zaretsky A, et al. Psychosocial interventions for bipolar disorder and coping style modification: similar clinical outcomes, similar mechanisms? *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2013 Aug;58(8):482-6. PMID: 23972110 **No eligible outcomes reported**
669. Parikh SV, LeBlanc SR, Ovanessian MM. Advancing bipolar disorder: key lessons from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2010 Mar;55(3):136-43. PMID: 20370963 **Ineligible study design**
670. Park LT, Lener MS, Hopkins M, et al. A double-blind, placebo-controlled, pilot study of riluzole monotherapy for acute bipolar depression. *Journal of Clinical Psychopharmacology*. 2017;37(3):355-8. doi: <http://dx.doi.org/10.1097/JCP.0000000000000693>. PMID: 615006763 **No eligible outcomes reported**
671. Patel R, Reiss P, Shetty H, et al. Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study. *BMJ Open*. 2015 Dec 14;5(12):e008341. doi: <http://dx.doi.org/10.1136/bmjopen-2015-008341>. PMID: 26667012 **Not treating bipolar**
672. Patino LR, Rummelhoff ER, Blom T, et al. A double-blind placebo-controlled study of exenatide for the treatment of weight gain associated with olanzapine in overweight or obese adults with bipolar disorder, major depressive disorder, schizophrenia or schizoaffective disorder. *Biological Psychiatry*. 2015 01 May;1):132S. PMID: 71846499 **Ineligible study design**
673. Patkar AA, Pae CU, Vohringer PA, et al. A 13-week, randomized double-blind, placebo-controlled, cross-over trial of ziprasidone in bipolar spectrum disorder. *Journal of Clinical Psychopharmacology*. 2015 13 Jun;35(3):319-23. doi: <http://dx.doi.org/10.1097/JCP.0000000000000323>. PMID: 25882763 (pubmed) 2015037995 (embase) **Not treating bipolar**
674. Pazzaglia PJ, George MS, Post RM, et al. Nimodipine increases CSF somatostatin in affectively ill patients. *Neuropsychopharmacology*. 1995 Aug;13(1):75-83. PMID: 8526973 **Bipolar not analyzed separately**
675. Pazzaglia PJ, Post RM, Ketter TA, et al. Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *Journal of Clinical Psychopharmacology*. 1998 Oct;18(5):404-13. PMID: 9790159 **Bipolar not analyzed separately**
676. Perlis RH, Adams DH, Fijal B, et al. Genetic association of treatment response with olanzapine/fluoxetine combination or lamotrigine in bipolar I depression. *Journal of Clinical Psychiatry*. 2010 2010;71(5):599-605. doi: <http://dx.doi.org/10.4088/JCP.08m04632gre>. **Ineligible study design**

677. Perlis RH, Sachs GS, Lafer B, et al. Effect of abrupt change from standard to low serum levels of lithium: a reanalysis of double-blind lithium maintenance data. *American Journal of Psychiatry*. 2002 Jul;159(7):1155-9. PMID: 12091193 **Ineligible study design**
678. Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *Journal of Clinical Psychiatry*. 2006 Apr;67(4):509-16. PMID: 16669715 **Ineligible study design**
679. Peters S, Pontin E, Lobban F, et al. Involving relatives in relapse prevention for bipolar disorder: a multi-perspective qualitative study of value and barriers. *BMC Psychiatry*. 2011;11:172. doi: <http://dx.doi.org/10.1186/1471-244X-11-172>. PMID: 22044486 **Ineligible study design**
680. Petrakis I, Ralevski E, Nich C, et al. Naltrexone and disulfiram in patients with alcohol dependence and current depression. *Journal of Clinical Psychopharmacology*. 2007 Apr;27(2):160-5. PMID: 17414239 **Not bipolar disorder**
681. Petrakis IL, Nich C, Ralevski E. Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophrenia Bulletin*. 2006 Oct;32(4):644-54. PMID: 16887890 **Bipolar not analyzed separately**
682. Petty F, Rush AJ, Davis JM, et al. Plasma GABA predicts acute response to divalproex in mania. *Biological Psychiatry*. 1996 Feb 15;39(4):278-84. PMID: 8645774 **No eligible outcomes reported**
683. Pfennig A, Bschor T, Falkai P, et al. The diagnosis and treatment of bipolar disorder: recommendations from the current s3 guideline. *Deutsches Arzteblatt International*. 2013 Feb;110(6):92-100. doi: <http://dx.doi.org/10.3238/arztebl.2013.0092>. PMID: 23451001 **Ineligible study design**
684. Pies R. Combining lithium and anticonvulsants in bipolar disorder: a review. *Annals of Clinical Psychiatry*. 2002 Dec;14(4):223-32. PMID: 12630658 **Ineligible study design**
685. Pikalov A, Tsai J, Mao Y, et al. Long-term use of lurasidone in patients with bipolar disorder: safety and effectiveness over 2 years of treatment. *International Journal of Bipolar Disorders*. 2017 01 Dec;5 (1) (no pagination)(9)doi: <http://dx.doi.org/10.1186/s40345-017-0075-7>. PMID: 614687852 **No eligible outcomes reported**
686. Pillay SS, Stoll AL, Weiss MK, et al. EEG abnormalities before clozapine therapy predict a good clinical response to clozapine. *Annals of Clinical Psychiatry*. 1996 Mar;8(1):1-5. PMID: 8743641 **Ineligible study design**
687. Pini S, Abelli M, Cassano GB. The role of quetiapine in the treatment of bipolar disorder. *Expert Opinion on Pharmacotherapy*. 2006 May;7(7):929-40. PMID: 16634715 **Ineligible study design**
688. Pompili M, Serafini G, Del Casale A, et al. Improving adherence in mood disorders: the struggle against relapse, recurrence and suicide risk. *Expert Review of Neurotherapeutics*. 2009 2009;9(7):985-1004. doi: <http://dx.doi.org/10.1586/ern.09.62>. **Ineligible study design**

689. Pompili M, Venturini P, Innamorati M, et al. The role of asenapine in the treatment of manic or mixed states associated with bipolar I disorder. *Neuropsychiatric Disease and Treatment*. 2011 6, 2011;7(1):259-65. **Ineligible study design**
690. Poole R, Simpson SA, Smith DJ. Internet-based psychoeducation for bipolar disorder: a qualitative analysis of feasibility, acceptability and impact. *BMC Psychiatry*. 2012;12:139. doi: <http://dx.doi.org/10.1186/1471-244X-12-139>. PMID: 22971042 **Ineligible study design**
691. Poolsup N, Li Wan Po A, de Oliveira IR. Systematic overview of lithium treatment in acute mania. *Journal of Clinical Pharmacy & Therapeutics*. 2000 Apr;25(2):139-56. PMID: 10849192 **Ineligible study design**
692. Pope M, Dudley R, Scott J. Determinants of social functioning in bipolar disorder. *Bipolar Disorders*. 2007 2007;9(1-2):38-44. doi: <http://dx.doi.org/10.1111/j.1399-5618.2007.00323.x>. **Ineligible study design**
693. Popovic D, Reinares M, Amann B, et al. Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder. *Psychopharmacology*. 2011 Feb;213(4):657-67. doi: <http://dx.doi.org/10.1007/s00213-010-2056-8>. PMID: 21052983 **Ineligible study design**
694. Popovic D, Torrent C, Goikolea JM, et al. Clinical implications of predominant polarity and the polarity index in bipolar disorder: a naturalistic study. *Acta Psychiatrica Scandinavica*. 2014 May;129(5):366-74. doi: <http://dx.doi.org/10.1111/acps.12179>. PMID: 23865756 **No eligible outcomes reported**
695. Post RM, Altshuler LL, Frye MA, et al. Rate of switch in bipolar patients prospectively treated with second-generation antidepressants as augmentation to mood stabilizers. *Bipolar Disorders*. 2001 Oct;3(5):259-65. PMID: 11912569 **Ineligible study design**
696. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline.[Erratum appears in *Br J Psychiatry*. 2006 Dec;189:569]. *British Journal of Psychiatry*. 2006 Aug;189:124-31. PMID: 16880481 **Ineligible study design**
697. Post RM, Denicoff KD, Leverich GS, et al. Drug-induced switching in bipolar disorder: Epidemiology and therapeutic implications. *CNS Drugs*. 1997 1997;8(5):352-65. doi: <http://dx.doi.org/10.2165/00023210-199708050-00002>. **Ineligible study design**
698. Post RM, Frye MA, Denicoff KD, et al. Emerging trends in the treatment of rapid cycling bipolar disorder: a selected review. *Bipolar Disorders*. 2000 Dec;2(4):305-15. PMID: 11252642 **Ineligible study design**
699. Post RM, Ketter TA, Denicoff K, et al. The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology*. 1996 Nov;128(2):115-29. PMID: 8956373 **Ineligible study design**
700. Post RM, Ketter TA, Pazzaglia PJ, et al. Rational polypharmacy in the bipolar affective disorders. *Epilepsy Research - Supplement*. 1996;11:153-80. PMID: 9294735 **Ineligible study design**
701. Post RM, Leverich GS, Nolen WA, et al. A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disorders*. 2003 Dec;5(6):396-406. PMID: 14636363 **Ineligible study design**

702. Praharaj SK, Jana AK, Goyal N, et al. Metformin for olanzapine-induced weight gain: a systematic review and meta-analysis. *British Journal of Clinical Pharmacology*. 2011 Mar;71(3):377-82. doi: <http://dx.doi.org/10.1111/j.1365-2125.2010.03783.x>. PMID: 21284696 **Ineligible study design**
703. Praharaj SK, Ram D, Arora M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: a randomized sham controlled study. *Journal of Affective Disorders*. 2009 Oct;117(3):146-50. doi: <http://dx.doi.org/10.1016/j.jad.2008.12.020>. PMID: 19178948 **Ineligible study design**
704. Pratoomsri W, Yatham LN, Bond DJ, et al. Oxcarbazepine in the treatment of bipolar disorder: a review. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2006 Jul;51(8):540-5. PMID: 16933591 **Ineligible study design**
705. Proudfoot J, Parker G, Manicavasagar V, et al. Effects of adjunctive peer support on perceptions of illness control and understanding in an online psychoeducation program for bipolar disorder: a randomised controlled trial. *Journal of Affective Disorders*. 2012 Dec 15;142(1-3):98-105. doi: <http://dx.doi.org/10.1016/j.jad.2012.04.007>. PMID: 22858215 **Ineligible study design**
706. Proudfoot JG, Jayawant A, Whittton AE, et al. Mechanisms underpinning effective peer support: a qualitative analysis of interactions between expert peers and patients newly-diagnosed with bipolar disorder. *BMC Psychiatry*. 2012;12:196. doi: <http://dx.doi.org/10.1186/1471-244X-12-196>. PMID: 23140497 **Ineligible study design**
707. Rabheru K. Maintenance electroconvulsive therapy (M-ECT) after acute response: examining the evidence for who, what, when, and how? *Journal of ECT*. 2012 Mar;28(1):39-47. doi: <http://dx.doi.org/10.1097/YCT.0b013e3182455758>. PMID: 22330700 **Ineligible study design**
708. Rajagopalan K, Bacci ED, Ng-Mak D, et al. Effects on health-related quality of life in patients treated with lurasidone for bipolar depression: Results from two placebo controlled bipolar depression trials. *BMC Psychiatry*. 2016 23 May;16 (1) (no pagination)(157)doi: <http://dx.doi.org/10.1186/s12888-016-0865-y>. PMID: 610427781 **No eligible outcomes reported**
709. Rakofsky JJ, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. *Journal of Clinical Psychiatry*. 2011 Jan;72(1):81-90. doi: <http://dx.doi.org/10.4088/JCP.09r05815gre>. PMID: 21208580 **Ineligible study design**
710. Rapinesi C, Bersani FS, Kotzalidis GD, et al. Maintenance deep transcranial magnetic stimulation sessions are associated with reduced depressive relapses in patients with unipolar or bipolar depression. *Frontiers in Neurology*. 2015;6(FEB)doi: <http://dx.doi.org/10.3389/fneur.2015.00016>. PMID: 2015896165 **Bipolar not analyzed separately**
711. Rasgon N. The relationship between polycystic ovary syndrome and antiepileptic drugs: a review of the evidence. *Journal of Clinical Psychopharmacology*. 2004 Jun;24(3):322-34. PMID: 15118487 **Ineligible study design**
712. Rasgon NL, Altshuler LL, Gudeman D, et al. Medication status and polycystic ovary syndrome in women with bipolar disorder: a preliminary report. *Journal of Clinical Psychiatry*. 2000 Mar;61(3):173-8. PMID: 10817101 **No eligible outcomes reported**

713. Redden L, Pritchett Y, Robieson W, et al. Suicidality and divalproex sodium: Analysis of controlled studies in multiple indications. *Annals of General Psychiatry*. 2011 18, 2011;10:1. doi: <http://dx.doi.org/10.1186/1744-859X-10-1>. **Ineligible study design**
714. Reinares M, Colom F, Sanchez-Moreno J, et al. Impact of caregiver group psychoeducation on the course and outcome of bipolar patients in remission: a randomized controlled trial.[Erratum appears in *Bipolar Disord*. 2008 Jul;10(5):657]. *Bipolar Disorders*. 2008 Jun;10(4):511-9. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00588.x>. PMID: 18452447 **Ineligible study design**
715. Reinares M, Rosa AR, Franco C, et al. A systematic review on the role of anticonvulsants in the treatment of acute bipolar depression. *International Journal of Neuropsychopharmacology*. 2013 Mar;16(2):485-96. doi: <http://dx.doi.org/10.1017/S1461145712000491>. PMID: 22575611 **Ineligible study design**
716. Reinares M, Vieta E, Colom F, et al. Impact of a psychoeducational family intervention on caregivers of stabilized bipolar patients. *Psychotherapy & Psychosomatics*. 2004 Sep-Oct;73(5):312-9. PMID: 15292629 **Not treating bipolar**
717. Rendell JM, Geddes JR. Risperidone in long-term treatment for bipolar disorder. *Cochrane Database of Systematic Reviews*. 2006(4):CD004999. PMID: 17054229 **Ineligible study design**
718. Rendell JM, Gijsman HJ, Bauer MS, et al. Risperidone alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2006(1):CD004043. PMID: 16437472 **Ineligible study design**
719. Rendell JM, Gijsman HJ, Keck P, et al. Olanzapine alone or in combination for acute mania. *Cochrane Database of Systematic Reviews*. 2003(3):CD004040. PMID: 12918000 **Ineligible study design**
720. Riemann D, Konig A, Hohagen F, et al. How to preserve the antidepressive effect of sleep deprivation: A comparison of sleep phase advance and sleep phase delay. *European Archives of Psychiatry & Clinical Neuroscience*. 1999;249(5):231-7. PMID: 10591988 **Ineligible study design**
721. Rifkin A, Doddi S, Karajgi B, et al. Dosage of haloperidol for mania. *British Journal of Psychiatry*. 1994 Jul;165(1):113-6. PMID: 7953013 **Bipolar not analyzed separately**
722. Rihmer Z, Gonda X. The effect of pharmacotherapy on suicide rates in bipolar patients. *CNS Neuroscience & Therapeutics*. 2012 Mar;18(3):238-42. doi: <http://dx.doi.org/10.1111/j.1755-5949.2011.00261.x>. PMID: 22070662 **Ineligible study design**
723. Rosa AR, Fountoulakis K, Siamouli M, et al. Is anticonvulsant treatment of mania a class effect? Data from randomized clinical trials. *CNS Neuroscience & Therapeutics*. 2011 Jun;17(3):167-77. doi: <http://dx.doi.org/10.1111/j.1755-5949.2009.00089.x>. PMID: 20015083 **Ineligible study design**
724. Rosenblatt JD, Kakar R, Berk M, et al. Anti-inflammatory agents in the treatment of bipolar depression: A systematic review and meta-analysis. *Bipolar Disorders*. 2016 01 Mar;18(2):89-101. doi: <http://dx.doi.org/10.1111/bdi.12373>. PMID: 609161232 **Ineligible study design**
725. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. *Journal of Clinical Psychiatry*. 1998;59 Suppl 5:32-9; discussion 40-1. PMID: 9635546 **Ineligible study design**
726. Royal A, New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar D. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Australian &*

- New Zealand Journal of Psychiatry. 2004 May;38(5):280-305. PMID: 15144505 **Ineligible study design**
727. Ruchlewska A, Mulder CL, Smulders R, et al. The effects of crisis plans for patients with psychotic and bipolar disorders: a randomised controlled trial. BMC Psychiatry. 2009;9:41. doi: <http://dx.doi.org/10.1186/1471-244X-9-41>. PMID: 19589145 **Ineligible study design**
728. Rusner M, Berg M, Begley C. Bipolar disorder in pregnancy and childbirth: A systematic review of outcomes. BMC Pregnancy and Childbirth. 2016 28 Oct;16 (1) (no pagination):331doi: <http://dx.doi.org/10.1186/s12884-016-1127-1>. PMID: 612941750 **Ineligible study design**
729. Sacchetti E, Galluzzo A, Valsecchi P. Oral ziprasidone in the treatment of patients with bipolar disorders: a critical review. Expert Review of Clinical Pharmacology. 2011 Mar;4(2):163-79. doi: <http://dx.doi.org/10.1586/ecp.10.139>. PMID: 22115400 **Ineligible study design**
730. Sachs G, Bowden C, Calabrese JR, et al. Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder. Bipolar Disorders. 2006 Apr;8(2):175-81. PMID: 16542188 **No eligible outcomes reported**
731. Sachs G, Chengappa KN, Suppes T, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disorders. 2004 Jun;6(3):213-23. PMID: 15117400 **Duplicate reference**
732. Sachs GS, Gardner-Schuster EE. Adjunctive treatment of acute mania: a clinical overview. Acta Psychiatrica Scandinavica, Supplementum. 2007(434):27-34. PMID: 17688460 **Ineligible study design**
733. Sachs GS, Gaulin BD, Gutierrez-Esteinou R, et al. Antimanic response to aripiprazole in bipolar I disorder patients is independent of the agitation level at baseline. Journal of Clinical Psychiatry. 2007 Sep;68(9):1377-83. PMID: 17915976 **Over 50% dropout rate**
734. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. American Journal of Psychiatry. 2002 Jul;159(7):1146-54. PMID: 12091192 **Over 50% dropout rate**
735. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. Journal of Clinical Psychiatry. 1994 Sep;55(9):391-3. PMID: 7929019 **Not treating bipolar**
736. Sachs GS, Thase ME. Bipolar disorder therapeutics: maintenance treatment. Biological Psychiatry. 2000 Sep 15;48(6):573-81. PMID: 11018228 **Ineligible study design**
737. Sajatovic M, Calabrese JR, Mullen J. Quetiapine for the treatment of bipolar mania in older adults. Bipolar Disorders. 2008 Sep;10(6):662-71. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00614.x>. PMID: 18837860 **Ineligible study design**
738. Sajatovic M, Davies M, Bauer MS, et al. Attitudes regarding the collaborative practice model and treatment adherence among individuals with bipolar disorder. Comprehensive Psychiatry. 2005 Jul-Aug;46(4):272-7. PMID: 16175758 **Ineligible study design**

739. Sajatovic M, Dines P, Fuentes-Casiano E, et al. Asenapine in the treatment of older adults with bipolar disorder. *International Journal of Geriatric Psychiatry*. 2015 01 Jul;30(7):710-9. doi: <http://dx.doi.org/10.1002/gps.4213>. PMID: 2015118224 **Ineligible study design**
740. Sajatovic M, Elhaj O, Youngstrom EA, et al. Treatment adherence in individuals with rapid cycling bipolar disorder: Results from a clinical-trial setting. *Journal of Clinical Psychopharmacology*. 2007 2007;27(4):412-4. doi: <http://dx.doi.org/10.1097/01.jcp.0000280310.50871.ff>. **Ineligible study design**
741. Sajatovic M, Gildengers A, Al Jurdi RK, et al. Multisite, open-label, prospective trial of lamotrigine for geriatric bipolar depression: A preliminary report. *Bipolar Disorders*. 2011 2011;13(3):294-302. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00923.x>. PMID: 21676132 **Ineligible study design**
742. Sajatovic M, Levin J, Tatsuoka C, et al. Customized adherence enhancement for individuals with bipolar disorder receiving antipsychotic therapy. *Psychiatric Services*. 2012 Feb 1;63(2):176-8. doi: <http://dx.doi.org/10.1176/appi.ps.201100133>. PMID: 22302337 **Ineligible study design**
743. Sajatovic M, Ramsay E, Nanry K, et al. Lamotrigine therapy in elderly patients with epilepsy, bipolar disorder or dementia. *International Journal of Geriatric Psychiatry*. 2007 Oct;22(10):945-50. PMID: 17326238 **Ineligible study design**
744. Sakinofsky I. Treating suicidality in depressive illness. Part 2: does treatment cure or cause suicidality? *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2007 Jun;52(6 Suppl 1):85S-101S. PMID: 17824355 **Ineligible study design**
745. Saksa JR, Baker CB, Woods SW. Mood-stabilizer-maintained, remitted bipolar patients: taper and discontinuation of adjunctive antipsychotic medication. *General Hospital Psychiatry*. 2004 May-Jun;26(3):233-6. PMID: 15121352 **Ineligible study design**
746. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Archives of General Psychiatry*. 2005 Jan;62(1):37-45. PMID: 15630071 **Over 50% dropout rate**
747. Salloum IM, Cornelius JR, Douaihy A, et al. Patient characteristics and treatment implications of marijuana abuse among bipolar alcoholics: results from a double blind, placebo-controlled study. *Addictive Behaviors*. 2005 Oct;30(9):1702-8. PMID: 16098680 **Ineligible study design**
748. Salvi V, Fagiolini A, Swartz HA, et al. The use of antidepressants in bipolar disorder. *Journal of Clinical Psychiatry*. 2008 Aug;69(8):1307-18. PMID: 18681751 **Ineligible study design**
749. Sampogna G, Del Vecchio V, Luciano M, et al. Efficacy of psychoeducational family intervention in bipolar I disorder: Results from a multicenter, randomized, controlled trial. *European Psychiatry*. 2015 31 Mar;30:554. PMID: 71931264 **Ineligible study design**
750. Sanchez-Moreno J, Bonnin C, Gonzalez-Pinto A, et al. Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. *European Neuropsychopharmacology*. 2017 April;27(4):350-9. doi: <http://dx.doi.org/10.1016/j.euroneuro.2017.01.010>. PMID: 614182952 **Ineligible study design**

751. Sanchez-Moreno J, Martinez-Aran A, Gadelrab HF, et al. The role and impact of contextual factors on functioning in patients with bipolar disorder. *Disability & Rehabilitation*. 2010;32 Suppl 1:S94-S104. doi: <http://dx.doi.org/10.3109/09638288.2010.520810>. PMID: 20883145 **Ineligible study design**
752. Sanford M, Keating GM. Quetiapine: a review of its use in the management of bipolar depression. *CNS Drugs*. 2012 May 1;26(5):435-60. doi: <http://dx.doi.org/10.2165/11203840-000000000-00000>. PMID: 22519923 **Ineligible study design**
753. Sanger TM, Tohen M, Vieta E, et al. Olanzapine in the acute treatment of bipolar I disorder with a history of rapid cycling. *Journal of Affective Disorders*. 2003 Jan;73(1-2):155-61. PMID: 12507748 **Over 50% dropout rate**
754. Saroukhani S, Emami-Parsa M, Modabbernia A, et al. Aspirin for treatment of lithium-associated sexual dysfunction in men: Randomized double-blind placebo-controlled study. *Bipolar Disorders*. 2013 2013;15(6):650-6. doi: <http://dx.doi.org/10.1111/bdi.12108>. **No eligible outcomes reported**
755. Sarris J, Lake J, Hoenders R. Bipolar disorder and complementary medicine: current evidence, safety issues, and clinical considerations. *Journal of Alternative & Complementary Medicine*. 2011 Oct;17(10):881-90. doi: <http://dx.doi.org/10.1089/acm.2010.0481>. PMID: 22010777 **Ineligible study design**
756. Schaffer A, Zuker P, Levitt A. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. *Journal of Affective Disorders*. 2006 Nov;96(1-2):95-9. PMID: 16820213 **Fewer than 11 subjects per arm**
757. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of General Psychiatry*. 2007 Apr;64(4):442-55. PMID: 17404121 **Ineligible study design**
758. Schottle D, Huber CG, Bock T, et al. Psychotherapy for bipolar disorder: a review of the most recent studies. *Current Opinion in Psychiatry*. 2011 Nov;24(6):549-55. doi: <http://dx.doi.org/10.1097/YCO.0b013e32834b7c5f>. PMID: 21918448 **Ineligible study design**
759. Scogin F, Morthland M, Kaufman A, et al. Improving quality of life in diverse rural older adults: a randomized trial of a psychological treatment. *Psychology & Aging*. 2007 Dec;22(4):657-65. doi: <http://dx.doi.org/10.1037/0882-7974.22.4.657>. PMID: 18179286 **Not bipolar disorder**
760. Scott J, Colom F. Psychosocial treatments for bipolar disorders. *Psychiatric Clinics of North America*. 2005 Jun;28(2):371-84. PMID: 15826737 **Ineligible study design**
761. Scott J, Colom F, Vieta E. A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. *International Journal of Neuropsychopharmacology*. 2007 Feb;10(1):123-9. PMID: 16787554 **Ineligible study design**
762. Scott J, Etain B. Which psychosocial interventions in bipolar depression? *Encephale*. 2011 Dec;37 Suppl 3:S214-7. doi: [http://dx.doi.org/10.1016/S0013-7006\(11\)70056-2](http://dx.doi.org/10.1016/S0013-7006(11)70056-2). PMID: 22212878 **Ineligible study design**
763. Searson R, Mansell W, Lowens I, et al. Think Effectively About Mood Swings (TEAMS): a case series of cognitive-behavioural therapy for bipolar disorders. *Journal of Behavior Therapy & Experimental*

Psychiatry. 2012 Jun;43(2):770-9. doi: <http://dx.doi.org/10.1016/j.jbtep.2011.10.001>. PMID: 22104659

Ineligible study design

764. Selten JP, Lundberg M, Rai D, et al. Risks for nonaffective psychotic disorder and bipolar disorder in young people with autism spectrum disorder: a population-based study. *JAMA Psychiatry*. 2015 May;72(5):483-9. doi: <http://dx.doi.org/10.1001/jamapsychiatry.2014.3059>. PMID: 25806797 **6**
Pediatric
765. Seo HJ, Chiesa A, Lee SJ, et al. Safety and tolerability of lamotrigine: results from 12 placebo-controlled clinical trials and clinical implications. *Clinical Neuropharmacology*. 2011 Jan-Feb;34(1):39-47. doi: <http://dx.doi.org/10.1097/WNF.0b013e3182055c07>. PMID: 21242744 **Ineligible study design**
766. Serafini G, Pompili M, Del Casale A, et al. Duloxetine versus venlafaxine in the treatment of unipolar and bipolar depression. *Clinica Terapeutica*. 2010;161(4):321-7. PMID: 20931154 **Bipolar not analyzed separately**
767. Serra G, Koukopoulos A, De Chiara L, et al. Three-year, naturalistic, mirror-image assessment of adding memantine to the treatment of 30 treatment-resistant patients with bipolar disorder. *Journal of Clinical Psychiatry*. 2015 Jan;76(1):e91-7. doi: <http://dx.doi.org/10.4088/JCP.13m08956>. PMID: 25650685
Ineligible study design
768. Serra G, Koukopoulos A, De Chiara L, et al. Features preceding diagnosis of bipolar versus major depressive disorders. *Journal of Affective Disorders*. 2015 Mar 1;173:134-42. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.050>. PMID: 25462407 **Ineligible study design**
769. Severus WE, Grunze H, Kleindienst N, et al. Is the prophylactic antidepressant efficacy of lithium in bipolar I disorder dependent on study design and lithium level? *Journal of Clinical Psychopharmacology*. 2005 Oct;25(5):457-62. PMID: 16160621 **Ineligible study design**
770. Severus WE, Kleindienst N, Seemuller F, et al. What is the optimal serum lithium level in the long-term treatment of bipolar disorder--a review? *Bipolar Disorders*. 2008 Mar;10(2):231-7. doi: <http://dx.doi.org/10.1111/j.1399-5618.2007.00475.x>. PMID: 18271901 **Ineligible study design**
771. Shafti SS, Shahveisi B. Comparison between lithium and valproate in the treatment of acute mania. *Journal of Clinical Psychopharmacology*. 2008 2008;28(6):718-20. doi: <http://dx.doi.org/10.1097/JCP.0b013e31818ce5ba>. **Ineligible study design**
772. Shakeri J, Khanegi M, Golshani S, et al. Effects of omega-3 supplement in the treatment of patients with bipolar I disorder. *International Journal of Preventive Medicine*. 2016(pagination)doi: <http://dx.doi.org/10.4103/2008-7802.182734>. PMID: 610426806 **Ineligible intervention**
773. Shan GW, Makmor-Bakry M, Omar MS. Long term use of lithium and factors associated with treatment response among patients with bipolar disorder. *Psychiatria Danubina*. 2016 Jun;28(2):146-53. PMID: 27287789 **No eligible outcomes reported**
774. Shansis FM, Reche M, Capp E. Evaluating response to mood stabilizers in patients with mixed depression: A study of agreement between three different mania rating scales and a depression rating scale. *Journal of Affective Disorders*. 2016 01 Jun;197:1-7. doi: <http://dx.doi.org/10.1016/j.jad.2016.02.064>. PMID: 608820721 **No eligible outcomes reported**

775. Sharma V, Sharma P. Peripartum-onset of obsessive-compulsive disorder in women with bipolar disorder - A case series. *Journal of Obsessive-Compulsive and Related Disorders*. 2015 July 01;6:120-3. doi: <http://dx.doi.org/10.1016/j.jocrd.2015.07.002>. PMID: 2015198049 **Ineligible study design**
776. Sharma V, Yatham LN, Haslam DR, et al. Continuation and prophylactic treatment of bipolar disorder. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 1997 Aug;42 Suppl 2:92S-100S. PMID: 9288442 **Ineligible study design**
777. Shashidhara M, Sushma BR, Viswanath B, et al. Comorbid obsessive compulsive disorder in patients with bipolar-I disorder. *Journal of Affective Disorders*. 2015 Mar 15;174:367-71. doi: <http://dx.doi.org/10.1016/j.jad.2014.12.019>. PMID: 25545603 **Ineligible intervention**
778. Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. *Journal of Clinical Psychiatry*. 2004 Dec;65(12):1715-9. PMID: 15641878 **Fewer than 11 subjects per arm**
779. Shen GH, Sylvia LG, Alloy LB, et al. Lifestyle regularity and cyclothymic symptomatology. *Journal of Clinical Psychology*. 2008 Apr;64(4):482-500. doi: <http://dx.doi.org/10.1002/jclp.20440>. PMID: 18322928 **No eligible outcomes reported**
780. Shi L, Namjoshi MA, Swindle R, et al. Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial.[Erratum appears in *Clin Ther*. 2004 Nov;26(11):1934]. *Clinical Therapeutics*. 2004 Jan;26(1):125-34. PMID: 14996525 **Ineligible study design**
781. Shi L, Schuh LM, Trzepacz PT, et al. Improvement of Positive and Negative Syndrome Scale cognitive score associated with olanzapine treatment of acute mania. *Current Medical Research & Opinion*. 2004 Sep;20(9):1371-6. PMID: 15383185 **No eligible outcomes reported**
782. Shine B, McKnight RF, Leaver L, et al. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015 Aug 1;386(9992):461-8. doi: [http://dx.doi.org/10.1016/S0140-6736\(14\)61842-0](http://dx.doi.org/10.1016/S0140-6736(14)61842-0). PMID: 26003379 **Ineligible study design**
783. Shopsin B, Gershon S, Thompson H, et al. Psychoactive drugs in mania. A controlled comparison of lithium carbonate, chlorpromazine, and haloperidol. *Arch Gen Psychiatry*. 1975 Jan;32(1):34-42. PMID: 1089401 **Fewer than 11 subjects per arm**
784. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *Journal of Clinical Psychiatry*. 2011 Feb;72(2):156-67. doi: <http://dx.doi.org/10.4088/JCP.09r05385gre>. PMID: 21034686 **Ineligible study design**
785. Sienaert P, Vansteelandt K, Demyttenaere K, et al. Ultra-brief pulse ECT in bipolar and unipolar depressive disorder: differences in speed of response. *Bipolar Disorders*. 2009 Jun;11(4):418-24. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00702.x>. PMID: 19500095 **No eligible outcomes reported**
786. Sikdar S, Kulhara P, Avasthi A, et al. Combined chlorpromazine and electroconvulsive therapy in mania. *British Journal of Psychiatry*. 1994 Jun;164(6):806-10. PMID: 7952988 **Bipolar not analyzed separately**

787. Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *Journal of Affective Disorders*. 2013 Apr 25;146(3):310-8. doi: <http://dx.doi.org/10.1016/j.jad.2012.11.001>. PMID: 23218251 **Ineligible study design**
788. Simhandl C, Konig B, Amann BL. A prospective 4-year naturalistic follow-up of treatment and outcome of 300 bipolar I and II patients. *Journal of Clinical Psychiatry*. 2014 Mar;75(3):254-62; quiz 63. doi: <http://dx.doi.org/10.4088/JCP.13m08601>. PMID: 24717379 **Ineligible study design**
789. Simhandl C, Radua J, Konig B, et al. The prevalence and effect of life events in 222 bipolar I and II patients: a prospective, naturalistic 4 year follow-up study. *Journal of Affective Disorders*. 2015 Jan 1;170:166-71. doi: <http://dx.doi.org/10.1016/j.jad.2014.08.043>. PMID: 25240845 **Ineligible intervention**
790. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *American Journal of Psychiatry*. 2004 Dec;161(12):2222-9. PMID: 15569893 **No eligible outcomes reported**
791. Simons W, Dierick M. Transcranial magnetic stimulation as a therapeutic tool in psychiatry. *World Journal of Biological Psychiatry*. 2005;6(1):6-25. PMID: 16097402 **Ineligible study design**
792. Simpson S, Barnes E, Griffiths E, et al. The Bipolar Interactive Psychoeducation (BIPED) study: trial design and protocol. *BMC Psychiatry*. 2009;9:50. doi: <http://dx.doi.org/10.1186/1471-244X-9-50>. PMID: 19674448 **Ineligible study design**
793. Singh JB, Zarate CA, Jr. Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials. *Bipolar Disorders*. 2006 Dec;8(6):696-709. PMID: 17156156 **Ineligible study design**
794. Small JG, Klapper MH, Marhenke JD, et al. Lithium combined with carbamazepine or haloperidol in the treatment of mania. *Psychopharmacology Bulletin*. 1995;31(2):265-72. PMID: 7491378 **Over 50% dropout rate**
795. Smith LA, Cornelius V, Warnock A, et al. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disorders*. 2007 Jun;9(4):394-412. PMID: 17547586 **Ineligible study design**
796. Smith LA, Cornelius V, Warnock A, et al. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. *Acta Psychiatrica Scandinavica*. 2007 Jan;115(1):12-20. PMID: 17201861 **Ineligible study design**
797. Smith LA, Cornelius V, Warnock A, et al. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disorders*. 2007 Sep;9(6):551-60. PMID: 17845269 **Ineligible study design**
798. Soares-Weiser K, Bravo Vergel Y, Beynon S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technology Assessment (Winchester, England)*. 2007 Oct;11(39):iii-iv, ix-206. PMID: 17903393 **Ineligible study design**

799. Sokolski KN. Adjunctive aripiprazole in bipolar I depression. *Annals of Pharmacotherapy*. 2007 Jan;41(1):35-40. PMID: 17190849 **Ineligible study design**
800. Solmi M, Veronese N, Zaninotto L, et al. Lamotrigine compared to placebo and other agents with antidepressant activity in patients with unipolar and bipolar depression: A comprehensive meta-analysis of efficacy and safety outcomes in short-term trials. *CNS Spectrums*. 2016 01 Oct;21(5):403-18. doi: <http://dx.doi.org/10.1017/S1092852916000523>. PMID: 612523889 **Ineligible study design**
801. Solomon DA, Keitner GI, Miller IW, et al. Course of illness and maintenance treatments for patients with bipolar disorder. *Journal of Clinical Psychiatry*. 1995 Jan;56(1):5-13. PMID: 7836345 **Ineligible study design**
802. Solomon DA, Keitner GI, Ryan CE, et al. Lithium plus valproate as maintenance polypharmacy for patients with bipolar I disorder: a review. *Journal of Clinical Psychopharmacology*. 1998 Feb;18(1):38-49. PMID: 9472841 **Ineligible study design**
803. Solomon DA, Ristow WR, Keller MB, et al. Serum lithium levels and psychosocial function in patients with bipolar I disorder. *American Journal of Psychiatry*. 1996 Oct;153(10):1301-7. PMID: 8831438 **Over 50% dropout rate**
804. Solomon DA, Ryan CE, Keitner GI, et al. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *J Clin Psychiatry*. 1997 Mar;58(3):95-9. PMID: 9108809 **Fewer than 11 subjects per arm**
805. Spaulding T, Westlund R, Thomason C, et al. Adjunctive treatment for mood stabilization of patients with bipolar I disorder treated with lamotrigine. *Cns Spectrums*. 2006 Sep;11(9):711-6; quiz 9. PMID: 16946696 **Ineligible study design**
806. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. *Epileptic Disorders*. 2004 Jun;6(2):57-75. PMID: 15246950 **Ineligible study design**
807. Srisurapanont M, Yatham LN, Zis AP. Treatment of acute bipolar depression: a review of the literature. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 1995 Nov;40(9):533-44. PMID: 8574989 **Ineligible study design**
808. Srivastava S, Ketter TA. Clinical relevance of treatments for acute bipolar disorder: balancing therapeutic and adverse effects. *Clinical Therapeutics*. 2011 Dec;33(12):B40-8. doi: <http://dx.doi.org/10.1016/j.clinthera.2011.11.020>. PMID: 22177379 **Ineligible study design**
809. Stahl S, Lombardo I, Loebel A, et al. Efficacy of ziprasidone in dysphoric mania: pooled analysis of two double-blind studies. *Journal of Affective Disorders*. 2010 Apr;122(1-2):39-45. doi: <http://dx.doi.org/10.1016/j.jad.2009.06.023>. PMID: 19616304 **Over 50% dropout rate**
810. Stange JP, Sylvia LG, da Silva Magalhaes PV, et al. Extreme attributions predict transition from depression to mania or hypomania in bipolar disorder. *Journal of Psychiatric Research*. 2013 2013;47(10):1329-36. doi: <http://dx.doi.org/10.1016/j.jpsychires.2013.05.016>. **Ineligible study design**
811. Stedman M, Pettinati HM, Brown ES, et al. A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. *Alcoholism: Clinical & Experimental Research*. 2010 Oct;34(10):1822-31. doi:

<http://dx.doi.org/10.1111/j.1530-0277.2010.01270.x>. PMID: 20626727 **No eligible outcomes reported**

812. Stoner SC, Nelson LA, Lea JW, et al. Historical review of carbamazepine for the treatment of bipolar disorder. *Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy*. 2007 Jan;27(1):68-88. PMID: 17192163 **Ineligible study design**
813. Stoner SC, Pace HA. Asenapine: a clinical review of a second-generation antipsychotic. *Clinical Therapeutics*. 2012 May;34(5):1023-40. doi: <http://dx.doi.org/10.1016/j.clinthera.2012.03.002>. PMID: 22494521 **Ineligible study design**
814. Storosum JG, Wohlfarth T, Gispens-de Wied CC, et al. Suicide risk in placebo-controlled trials of treatment for acute manic episode and prevention of manic-depressive episode. *American Journal of Psychiatry*. 2005 Apr;162(4):799-802. PMID: 15800158 **Ineligible study design**
815. Suppes T. Review of the use of topiramate for treatment of bipolar disorders. *Journal of Clinical Psychopharmacology*. 2002 Dec;22(6):599-609. PMID: 12454560 **Ineligible study design**
816. Suppes T, Brown E, Schuh LM, et al. Rapid versus non-rapid cycling as a predictor of response to olanzapine and divalproex sodium for bipolar mania and maintenance of remission: post hoc analyses of 47-week data. *Journal of Affective Disorders*. 2005 Dec;89(1-3):69-77. PMID: 16253344 **Over 50% dropout rate**
817. Suppes T, Eudicone J, McQuade R, et al. Efficacy and safety of aripiprazole in subpopulations with acute manic or mixed episodes of bipolar I disorder. *Journal of Affective Disorders*. 2008 Apr;107(1-3):145-54. PMID: 17904226 **Over 50% dropout rate**
818. Suppes T, Kelly DI, Hynan LS, et al. Comparison of two anticonvulsants in a randomized, single-blind treatment of hypomanic symptoms in patients with bipolar disorder. *Australian & New Zealand Journal of Psychiatry*. 2007 May;41(5):397-402. PMID: 17464731 **Fewer than 11 subjects per arm**
819. Suppes T, Ketter TA, Gwizdowski IS, et al. First controlled treatment trial of bipolar II hypomania with mixed symptoms: quetiapine versus placebo. *Journal of Affective Disorders*. 2013 Aug 15;150(1):37-43. doi: <http://dx.doi.org/10.1016/j.jad.2013.02.031>. PMID: 23521871 **Over 50% dropout rate**
820. Suppes T, Marangell LB, Bernstein IH, et al. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. *Journal of Affective Disorders*. 2008 Dec;111(2-3):334-43. doi: <http://dx.doi.org/10.1016/j.jad.2008.02.004>. PMID: 18358540 **Over 50% dropout rate**
821. Suppes T, Rush AJ, Dennehy EB, et al. Texas Medication Algorithm Project, phase 3 (TMAP-3): clinical results for patients with a history of mania. *Journal of Clinical Psychiatry*. 2003 Apr;64(4):370-82. PMID: 12716236 **Ineligible intervention**
822. Suppes T, Rush AJ, Jr., Kraemer HC, et al. Treatment algorithm use to optimize management of symptomatic patients with a history of mania. *Journal of Clinical Psychiatry*. 1998 Feb;59(2):89-96; quiz 7-8. PMID: 9501899 **Ineligible study design**
823. Suppes T, Webb A, Paul B, et al. Clinical outcome in a randomized 1-year trial of clozapine versus treatment as usual for patients with treatment-resistant illness and a history of mania. *American Journal of Psychiatry*. 1999 Aug;156(8):1164-9. PMID: 10450255 **Bipolar not analyzed separately**

824. Sussman N, Mullen J, Paulsson B, et al. Rates of remission/euthymia with quetiapine in combination with lithium/divalproex for the treatment of acute mania. *Journal of Affective Disorders*. 2007;100 Suppl 1:S55-63. PMID: 17383736 **Duplicate reference**
825. Swainston Harrison T, Keating GM. Extended-release carbamazepine capsules : in bipolar I disorder. *CNS Drugs*. 2005;19(8):709-16. PMID: 16097852 **Ineligible study design**
826. Swann AC, Bowden CL, Calabrese JR, et al. Differential effect of number of previous episodes of affective disorder on response to lithium or divalproex in acute mania. *American Journal of Psychiatry*. 1999 Aug;156(8):1264-6. PMID: 10450271 **Ineligible study design**
827. Swann AC, Bowden CL, Calabrese JR, et al. Mania: differential effects of previous depressive and manic episodes on response to treatment. *Acta Psychiatrica Scandinavica*. 2000 Jun;101(6):444-51. PMID: 10868467 **Ineligible study design**
828. Swann AC, Bowden CL, Morris D, et al. Depression during mania. Treatment response to lithium or divalproex. *Archives of General Psychiatry*. 1997 Jan;54(1):37-42. PMID: 9006398 **Bipolar not analyzed separately**
829. Swann AC, Petty F, Bowden CL, et al. Mania: gender, transmitter function, and response to treatment. *Psychiatry Research*. 1999 Oct 18;88(1):55-61. PMID: 10641586 **No eligible outcomes reported**
830. Swartz HA, Frank E. Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disorders*. 2001 Feb;3(1):11-22. PMID: 11256459 **Ineligible study design**
831. Swartz HA, Frank E, Cheng Y. A randomized pilot study of psychotherapy and quetiapine for the acute treatment of bipolar II depression. *Bipolar Disorders*. 2012 Mar;14(2):211-6. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.00988.x>. PMID: 22420597 **Less than 11 subjects per arm**
832. Sylvia LG, Ametrano RM, Nierenberg AA. Exercise treatment for bipolar disorder: potential mechanisms of action mediated through increased neurogenesis and decreased allostatic load. *Psychotherapy & Psychosomatics*. 2010;79(2):87-96. doi: <http://dx.doi.org/10.1159/000270916>. PMID: 20051706 **Ineligible study design**
833. Sylvia LG, Peters AT, Deckersbach T, et al. Nutrient-based therapies for bipolar disorder: A systematic review. *Psychotherapy and Psychosomatics*. 2012 2012;82(1):10-9. doi: <http://dx.doi.org/10.1159/000341309>. **Ineligible study design**
834. Sylvia LG, Rabideau DJ, Nierenberg AA, et al. The effect of personalized guideline-concordant treatment on quality of life and functional impairment in bipolar disorder. *Journal of Affective Disorders*. 2014 1, 2014;169:144-8. doi: <http://dx.doi.org/10.1016/j.jad.2014.08.019>. PMID: 25194782 **Ineligible intervention**
835. Sylvia LG, Shelton RC, Kemp DE, et al. Medical burden in bipolar disorder: Findings from the Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder study (Bipolar CHOICE). *Bipolar Disorders*. 2015 01 Mar;17(2):212-23. doi: <http://dx.doi.org/10.1111/bdi.12243>. **Not treating bipolar**

836. Szegedi A, Zhao J, McIntyre RS. Early improvement as a predictor of acute treatment outcome in manic or mixed episodes in bipolar-I disorder: A pooled, post hoc analysis from the asenapine development program. *Journal of Affective Disorders*. 2013 25, 2013;150(3):745-52. doi: <http://dx.doi.org/10.1016/j.jad.2013.01.024>. **Ineligible study design**
837. Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101. doi: <http://dx.doi.org/10.1186/1471-244X-11-101>. PMID: 21689438 **Ineligible study design**
838. Szentagotai A, David D. The efficacy of cognitive-behavioral therapy in bipolar disorder: a quantitative meta-analysis. *Journal of Clinical Psychiatry*. 2010 Jan;71(1):66-72. doi: <http://dx.doi.org/10.4088/JCP.08r04559yel>. PMID: 19852904 **Ineligible study design**
839. Szuba MP, Amsterdam JD. Rapid Antidepressant Response After Nocturnal TRH Administration in Patients With Bipolar Type I and Bipolar Type II Major Depression. *Journal of Clinical Psychopharmacology*. 2005 2005;25(4):325-30. doi: <http://dx.doi.org/10.1097/01.jcp.0000169037.17884.79>. **No eligible outcomes reported**
840. Tada M, Uchida H, Mizushima J, et al. Antidepressant dose and treatment response in bipolar depression: Reanalysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) data. *Journal of Psychiatric Research*. 2015 01 Sep;68:151-6. doi: <http://dx.doi.org/10.1016/j.jpsychires.2015.06.015>. PMID: 2015230798 **Ineligible intervention**
841. Tamayo JM, Mazzotti G, Tohen M, et al. Outcomes for Latin American versus White patients suffering from acute mania in a randomized, double-blind trial comparing olanzapine and haloperidol. *Journal of Clinical Psychopharmacology*. 2007 Apr;27(2):126-34. PMID: 17414234 **Duplicate reference**
842. Tamayo JM, Mejia-Rodriguez D, Navarro-Montoya AM, et al. Therapy of No-Type I bipolar spectrum disorders: A systematic review. *Current Psychiatry Reviews*. 2013 2013;9(1):41-50. **Ineligible study design**
843. Tamayo JM, Sutton VK, Mattei MA, et al. Effectiveness and safety of the combination of fluoxetine and olanzapine in outpatients with bipolar depression: an open-label, randomized, flexible-dose study in Puerto Rico. *Journal of Clinical Psychopharmacology*. 2009 Aug;29(4):358-61. doi: <http://dx.doi.org/10.1097/JCP.0b013e3181ad223f>. PMID: 19593175 **Ineligible study design**
844. Tamayo JM, Zarate CA, Jr., Vieta E, et al. Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*. 2010 Jul;13(6):813-32. doi: <http://dx.doi.org/10.1017/S1461145709991246>. PMID: 20128953 **Ineligible study design**
845. Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania--a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011 Nov;134(1-3):14-9. doi: <http://dx.doi.org/10.1016/j.jad.2010.11.009>. PMID: 21145595 **Ineligible study design**
846. Thase ME. Quetiapine monotherapy for bipolar depression. *Neuropsychiatric Disease and Treatment*. 2008;4(1A):21-31. doi: <http://dx.doi.org/10.2147/NDT.S1162>. **Ineligible study design**

847. Thase ME, Bowden CL, Nashat M, et al. Aripiprazole in bipolar depression: a pooled, post-hoc analysis by severity of core depressive symptoms. *International Journal of Psychiatry in Clinical Practice*. 2012 Jun;16(2):121-31. doi: <http://dx.doi.org/10.3109/13651501.2011.632680>. PMID: 22296512 **Ineligible study design**
848. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies.[Erratum appears in *J Clin Psychopharmacol*. 2009 Feb;29(1):38]. *Journal of Clinical Psychopharmacology*. 2008 Feb;28(1):13-20. doi: <http://dx.doi.org/10.1097/jcp.0b013e3181618eb4>. PMID: 18204335 **No eligible outcomes reported**
849. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of Quetiapine Monotherapy in Bipolar I and II Depression: A Double-blind, Placebo-controlled Study (The BOLDER II Study). *Journal of Clinical Psychopharmacology*. 2006 2006;26(6):600-9. doi: <http://dx.doi.org/10.1097/01.jcp.0000248603.76231.b7>. **No eligible outcomes reported**
850. Thirthalli J, Prasad MK, Gangadhar BN. Electroconvulsive therapy (ECT) in bipolar disorder: A narrative review of literature. *Asian Journal of Psychiatry*. 2012 2012;5(1):11-7. doi: <http://dx.doi.org/10.1016/j.ajp.2011.12.002>. **Ineligible study design**
851. Todd NJ, Solis-Trapala I, Jones SH, et al. An online randomised controlled trial to assess the feasibility, acceptability and potential effectiveness of 'Living with Bipolar': a web-based self-management intervention for bipolar disorder: trial design and protocol. *Contemporary Clinical Trials*. 2012 Jul;33(4):679-88. doi: <http://dx.doi.org/10.1016/j.cct.2012.02.011>. PMID: 22387150 **Ineligible study design**
852. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania. *The American Journal of Psychiatry*. 2002 2002;159(6):1011-7. doi: <http://dx.doi.org/10.1176/appi.ajp.159.6.1011>. **Duplicate reference**
853. Tohen M, Sanger TM, McElroy SL, et al. Olanzapine versus placebo in the treatment of acute mania. *The American Journal of Psychiatry*. 1999 1999;156(5):702-9. PMID: 10327902 **Over 50% dropout rate**
854. Tohen M, Sniadecki J, Sutton VK, et al. Number needed to treat or harm analyses of olanzapine for maintenance treatment of bipolar disorder. *Journal of Clinical Psychopharmacology*. 2009 Dec;29(6):520-8. doi: <http://dx.doi.org/10.1097/JCP.0b013e3181bfe128>. PMID: 19910715 **Ineligible study design**
855. Tohen M, Sutton VK, Calabrese JR, et al. Maintenance of response following stabilization of mixed index episodes with olanzapine monotherapy in a randomized, double-blind, placebo-controlled study of bipolar I disorder. *Journal of Affective Disorders*. 2009 Jul;116(1-2):43-50. doi: <http://dx.doi.org/10.1016/j.jad.2008.11.003>. PMID: 19054570 **Over 50% dropout rate**
856. Tohen M, Zarate CA, Jr. Antipsychotic agents and bipolar disorder. *Journal of Clinical Psychiatry*. 1998;59 Suppl 1:38-48; discussion 9. PMID: 9448668 **Ineligible study design**
857. Tolliver BK, Desantis SM, Brown DG, et al. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. *Bipolar Disorders*. 2012 Feb;14(1):54-63. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00973.x>. PMID: 22329472 **No eligible outcomes reported**

858. Tolliver BK, McRae AL, Verduin ML, et al. Reversible elevation of triglycerides in dual-diagnosis patients taking aripiprazole: A case series. *Journal of Clinical Psychopharmacology*. 2008 2008;28(4):464-7. doi: <http://dx.doi.org/10.1097/JCP.0b013e31817efb99>. PMID: 18626281 **Ineligible study design**
859. Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. *British Journal of Psychiatry - Supplementum*. 2001 Jun;41:s184-90. PMID: 11450181 **Ineligible study design**
860. Torrent C, Bonnin Cdel M, Martinez-Aran A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *American Journal of Psychiatry*. 2013 Aug 1;170(8):852-9. doi: <http://dx.doi.org/10.1176/appi.ajp.2012.12070971>. PMID: 23511717 **Ineligible study design**
861. Torrey EF, Davis JM. Adjunct treatments for schizophrenia and bipolar disorder: what to try when you are out of ideas. *Clinical Schizophrenia & Related Psychoses*. 2012 Jan;5(4):208-16. doi: <http://dx.doi.org/10.3371/CSRP.5.4.5>. PMID: 22182458 **Ineligible study design**
862. Tsai AC, Rosenlicht NZ, Jureidini JN, et al. Aripiprazole in the maintenance treatment of bipolar disorder: a critical review of the evidence and its dissemination into the scientific literature. *PLoS Medicine / Public Library of Science*. 2011 May;8(5):e1000434. doi: <http://dx.doi.org/10.1371/journal.pmed.1000434>. PMID: 21559324 **Ineligible study design**
863. Tseng PT, Chen YW, Tu KY, et al. Light therapy in the treatment of patients with bipolar depression: A meta-analytic study. *European Neuropsychopharmacology*. 2016 01 Jun;26(6):1037-47. doi: <http://dx.doi.org/10.1016/j.euroneuro.2016.03.001>. PMID: 609105359 **Ineligible study design**
864. Tundo A, Calabrese JR, Proietti L, et al. Variation in response to short-term antidepressant treatment between patients with continuous and non-continuous cycling bipolar disorders. *Journal of Affective Disorders*. 2015 Mar 15;174:126-30. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.036>. PMID: 25497468 **Not treating bipolar**
865. Ukaegbu C, Banks JB, Carter NJ. What drugs are best for bipolar depression? [References]. *The Journal of Family Practice*. 2008 2008;57(9):606-8. **Ineligible study design**
866. Uleickas Yood M, Delorenze G, Quesenberry CP, Jr., et al. Epidemiologic study of aripiprazole use and the incidence of suicide events. *Pharmacoeconomics & Drug Safety*. 2010 Nov;19(11):1124-30. doi: <http://dx.doi.org/10.1002/pds.2047>. PMID: 20925132 **Bipolar not analyzed separately**
867. Ummer S, Dorai B, Ramanathan S. Distressing cutaneous lesion among bipolar affective disorder patients on lithium therapy: A retrospective cross-sectional study. *Indian Journal of Psychiatry*. 2016 October-December;58(4):383-6. doi: <http://dx.doi.org/10.4103/0019-5545.196708>. PMID: 614018225 **No eligible outcomes reported**
868. Unholzer S, Haen E. Retrospective analysis of therapeutic drug monitoring data for treatment of bipolar disorder with lamotrigine.[Erratum appears in *Pharmacopsychiatry*. 2015 Nov;48(7):296; PMID: 26630654]. *Pharmacopsychiatry*. 2015 Sep;48(6):211-4. doi: <http://dx.doi.org/10.1055/s-0035-1559635>. PMID: 26252722 **Ineligible study design**
869. Valenti M, Benabarre A, Garcia-Amador M, et al. Electroconvulsive therapy in the treatment of mixed states in bipolar disorder. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2008 Jan;23(1):53-6. doi: <http://dx.doi.org/10.1016/j.eurpsy.2007.10.011>. PMID: 18191551 **Ineligible study design**

870. Valenti M, Pacchiarotti I, Undurraga J, et al. Risk factors for rapid cycling in bipolar disorder. *Bipolar Disorders*. 2015 01 Aug;17(5):549-59. doi: <http://dx.doi.org/10.1111/bdi.12288>. PMID: 2015769954
Ineligible study design
871. van der Loos ML, Mulder P, Hartong EG, et al. Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine. *Acta Psychiatrica Scandinavica*. 2010 Sep;122(3):246-54. doi: <http://dx.doi.org/10.1111/j.1600-0447.2009.01537.x>. PMID: 20136801 **No eligible outcomes reported**
872. van der Loos ML, Mulder P, Hartong EG, et al. Long-term outcome of bipolar depressed patients receiving lamotrigine as add-on to lithium with the possibility of the addition of paroxetine in nonresponders: a randomized, placebo-controlled trial with a novel design. *Bipolar Disorders*. 2011 Feb;13(1):111-7. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00887.x>. PMID: 21320258 **No eligible outcomes reported**
873. van der Loos ML, Mulder PG, Hartong EG, et al. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*. 2009 Feb;70(2):223-31. PMID: 19200421 **Ineligible study design**
874. van der Voort TY, van Meijel B, Goossens PJ, et al. Collaborative care for patients with bipolar disorder: a randomised controlled trial. *BMC Psychiatry*. 2011;11:133. doi: <http://dx.doi.org/10.1186/1471-244X-11-133>. PMID: 21849078 **Ineligible study design**
875. Van Dijk S, Jeffrey J, Katz MR. A randomized, controlled, pilot study of dialectical behavior therapy skills in a psychoeducational group for individuals with bipolar disorder. *Journal of Affective Disorders*. 2013 Mar 5;145(3):386-93. doi: <http://dx.doi.org/10.1016/j.jad.2012.05.054>. PMID: 22858264 **Ineligible intervention**
876. Van Lieshout RJ, MacQueen GM. Efficacy and acceptability of mood stabilisers in the treatment of acute bipolar depression: systematic review. *British Journal of Psychiatry*. 2010 Apr;196(4):266-73. doi: <http://dx.doi.org/10.1192/bjp.bp.108.057612>. PMID: 20357301 **Ineligible study design**
877. Vasudev A, Macritchie K, Rao SK, et al. Tiagabine for acute affective episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*. 2012;12:CD004694. doi: <http://dx.doi.org/10.1002/14651858.CD004694.pub3>. PMID: 23235614 **Ineligible study design**
878. Vasudev A, Macritchie K, Rao SN, et al. Tiagabine in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews*. 2011(12):CD005173. doi: <http://dx.doi.org/10.1002/14651858.CD005173.pub3>. PMID: 22161389 **Ineligible study design**
879. Vasudev A, Macritchie K, Vasudev K, et al. Oxcarbazepine for acute affective episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*. 2011(12):CD004857. doi: <http://dx.doi.org/10.1002/14651858.CD004857.pub2>. PMID: 22161387 **Ineligible study design**
880. Vasudev A, Macritchie K, Watson S, et al. Oxcarbazepine in the maintenance treatment of bipolar disorder. *Cochrane Database of Systematic Reviews*. 2008(1):CD005171. doi: <http://dx.doi.org/10.1002/14651858.CD005171.pub2>. PMID: 18254071 **Ineligible study design**

881. Vasudev K, Macritchie K, Geddes J, et al. Topiramate for acute affective episodes in bipolar disorder. Cochrane Database of Systematic Reviews. 2006(1):CD003384. PMID: 16437453 **Ineligible study design**
882. Vazquez GH, Tondo L, Undurraga J, et al. Overview of antidepressant treatment of bipolar depression. International Journal of Neuropsychopharmacology. 2013 Aug;16(7):1673-85. doi: <http://dx.doi.org/10.1017/S1461145713000023>. PMID: 23428003 **Ineligible study design**
883. Vedula SS, Bero L, Scherer RW, et al. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. New England Journal of Medicine. 2009 Nov 12;361(20):1963-71. doi: <http://dx.doi.org/10.1056/NEJMs0906126>. PMID: 19907043 **Ineligible study design**
884. Veeh J, Kopf J, Kittel-Schneider S, et al. Cognitive remediation for bipolar patients with objective cognitive impairment: a naturalistic study. International Journal of Bipolar Disorders. 2017 01 Dec;5 (1) (no pagination)(8)doi: <http://dx.doi.org/10.1186/s40345-017-0079-3>. PMID: 615340856 **Ineligible study design**
885. Versiani M, Cheniaux E, Landeira-Fernandez J. Efficacy and safety of electroconvulsive therapy in the treatment of bipolar disorder: a systematic review. Journal of ECT. 2011 Jun;27(2):153-64. doi: <http://dx.doi.org/10.1097/YCT.0b013e3181e6332e>. PMID: 20562714 **Ineligible study design**
886. Vieta E, Calabrese JR, Hennen J, et al. Comparison of rapid-cycling and non-rapid-cycling bipolar I manic patients during treatment with olanzapine: analysis of pooled data. Journal of Clinical Psychiatry. 2004 Oct;65(10):1420-8. PMID: 15491248 **Over 50% dropout rate**
887. Vieta E, Durgam S, Lu K, et al. Effect of cariprazine across the symptoms of mania in bipolar I disorder: Analyses of pooled data from phase II/III trials. European Neuropsychopharmacology. 2015 Nov;25(11):1882-91. doi: <http://dx.doi.org/10.1016/j.euroneuro.2015.08.020>. PMID: 26419293 **Duplicate reference**
888. Vieta E, Goldberg JF, Mullen J, et al. Quetiapine in the treatment of acute mania: target dose for efficacious treatment. Journal of Affective Disorders. 2007;100 Suppl 1:S23-31. PMID: 17382403 **Ineligible study design**
889. Vieta E, Gunther O, Locklear J, et al. Effectiveness of psychotropic medications in the maintenance phase of bipolar disorder: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology. 2011 Sep;14(8):1029-49. doi: <http://dx.doi.org/10.1017/S1461145711000885>. PMID: 21733231 **Ineligible study design**
890. Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. Journal of Clinical Psychopharmacology. 2010 Oct;30(5):579-90. doi: <http://dx.doi.org/10.1097/JCP.0b013e3181f15849>. PMID: 20814319 **Ineligible study design**
891. Vieta E, Martinez-Aran A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. Journal of Clinical Psychiatry. 2002 Jun;63(6):508-12. PMID: 12088162 **Ineligible study design**
892. Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. Current Medical Research & Opinion. 2005 Jun;21(6):923-34. PMID: 15969892 **Duplicate reference**

893. Vieta E, Ramey T, Keller D, et al. Ziprasidone in the treatment of acute mania: a 12-week, placebo-controlled, haloperidol-referenced study. *Journal of Psychopharmacology*. 2010 Apr;24(4):547-58. doi: <http://dx.doi.org/10.1177/0269881108099418>. PMID: 19074536 **Over 50% dropout rate**
894. Vieta E, Suppes T, Ekholm B, et al. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. *Journal of Affective Disorders*. 2012 Dec 15;142(1-3):36-44. doi: <http://dx.doi.org/10.1016/j.jad.2012.04.014>. PMID: 23062763 **Over 50% dropout rate**
895. Vik A, Ravindran A, Shiah IS, et al. A double-blind, placebo-controlled study of adjunctive calcitonin nasal spray in acute refractory mania. *Bipolar Disorders*. 2013 2013;15(4):359-64. PMID: 23551803 **Over 50% dropout rate**
896. Vik A, Yatham LN. Calcitonin and bipolar disorder: a hypothesis revisited. *Journal of Psychiatry & Neuroscience*. 1998 Mar;23(2):109-17. PMID: 9549251 **Ineligible study design**
897. Viktorin A, Ryden E, Thase ME, et al. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. *American Journal of Psychiatry*. 2017 01 Apr;174(4):341-8. doi: <http://dx.doi.org/10.1176/appi.ajp.2016.16040467>. PMID: 27690517 PMID/615229531 Embase **No eligible outcomes reported**
898. Visser HM, Van Der Mast RC. Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review. *World Journal of Biological Psychiatry*. 2005;6(4):231-41. PMID: 16272078 **Ineligible study design**
899. Vita A, De Peri L, Siracusano A, et al. Efficacy and tolerability of asenapine for acute mania in bipolar I disorder: Meta-analyses of randomized-controlled trials. *International Clinical Psychopharmacology*. 2013 2013;28(5):219-27. doi: <http://dx.doi.org/10.1097/YIC.0b013e32836290d2>. **Ineligible study design**
900. Vohringer PA, Ostacher MJ, El-Mallakh RS, et al. Antidepressants in Type II Versus Type I Bipolar Depression: A Randomized Discontinuation Trial. *Journal of Clinical Psychopharmacology*. 2015 12 Oct;35(5):605-8. doi: <http://dx.doi.org/10.1097/JCP.0000000000000384>. PMID: 2015371706 **Over 50% dropout rate**
901. Walton SA, Berk M, Brook S. Superiority of lithium over verapamil in mania: a randomized, controlled, single-blind trial. *Journal of Clinical Psychiatry*. 1996 Nov;57(11):543-6. PMID: 8968305 **Not treating bipolar**
902. Wang PW, Ketter TA. Clinical use of carbamazepine for bipolar disorders. *Expert Opinion on Pharmacotherapy*. 2005 Dec;6(16):2887-902. PMID: 16318439 **Ineligible study design**
903. Wang PW, Ketter TA, Becker OV, et al. New anticonvulsant medication uses in bipolar disorder. *Cns Spectrums*. 2003 Dec;8(12):930-2, 41-7. PMID: 14978468 **Ineligible study design**
904. Wang Z, Gao K, Kemp DE, et al. Lamotrigine adjunctive therapy to lithium and divalproex in depressed patients with rapid cycling bipolar disorder and a recent substance use disorder: a 12-week, double-blind, placebo-controlled pilot study. *Psychopharmacology Bulletin*. 2010;43(4):5-21. PMID: 21240149 **Over 50% dropout rate**

905. Warrington L, Lombardo I, Loebel A, et al. Ziprasidone for the treatment of acute manic or mixed episodes associated with bipolar disorder. *CNS Drugs*. 2007;21(10):835-49. PMID: 17850172 **Ineligible study design**
906. Watson S, Gallagher P, Porter RJ, et al. A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. *Biological Psychiatry*. 2012 Dec 1;72(11):943-9. doi: <http://dx.doi.org/10.1016/j.biopsych.2012.05.029>. PMID: 22770649 **No eligible outcomes reported**
907. Weber B, Jermann F, Gex-Fabry M, et al. Mindfulness-based cognitive therapy for bipolar disorder: a feasibility trial. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2010 Oct;25(6):334-7. doi: <http://dx.doi.org/10.1016/j.eurpsy.2010.03.007>. PMID: 20561769 **No eligible outcomes reported**
908. Weisler RH. Carbamazepine extended-release capsules in bipolar disorder. *Neuropsychiatric Disease and Treatment*. 2006 2006;2(1):3-11. **Ineligible study design**
909. Weisler RH, Kalali AH, Cutler AJ, et al. Efficacy and safety of once- versus twice-daily carbamazepine extended-release capsules for the treatment of manic symptoms in patients with bipolar I disorder. *Psychiatry*. 2008 2008;5(3):35-48. PMID: 22778707 **Over 50% dropout rate**
910. Weisler RH, Kalali AH, Ketter TA, et al. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *Journal of Clinical Psychiatry*. 2004 Apr;65(4):478-84. PMID: 15119909 **Over 50% dropout rate**
911. Weisler RH, Keck PE, Jr., Swann AC, et al. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial.[Erratum appears in *J Clin Psychiatry*. 2005 May;66(5):659]. *Journal of Clinical Psychiatry*. 2005 Mar;66(3):323-30. PMID: 15766298 **Duplicate reference**
912. Welge JA, Keck PE, Jr., Meinhold JM. Predictors of response to treatment of acute bipolar manic episodes with divalproex sodium or placebo in 2 randomized, controlled, parallel-group trials. *Journal of Clinical Psychopharmacology*. 2004 Dec;24(6):607-12. PMID: 15538121 **Ineligible study design**
913. Welten CC, Koeter MW, Wohlfarth TD, et al. Does Insight Affect the Efficacy of Antipsychotics in Acute Mania?: An Individual Patient Data Regression Meta-Analysis. *Journal of Clinical Psychopharmacology*. 2016 Feb;36(1):71-6. doi: <http://dx.doi.org/10.1097/JCP.0000000000000435>. PMID: 26647231 **No eligible outcomes reported**
914. Welten CCM, Koeter MWJ, Wohlfarth TD, et al. Early nonresponse in the antipsychotic treatment of acute mania: A criterion for reconsidering treatment? Results from an individual patient data Meta-Analysis. *Journal of Clinical Psychiatry*. 2016 September;77(9):e1117-e23. doi: <http://dx.doi.org/10.4088/JCP.15r10051>. PMID: 612499219 **Ineligible study design**
915. Wesseloo R, Liu X, Clark CT, et al. Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study. *Journal of Affective Disorders*. 2017 15 Aug;218:394-7. doi: <http://dx.doi.org/10.1016/j.jad.2017.04.070>. PMID: 616031023 **No eligible outcomes reported**

916. Wheeler AL, Wessa M, Szeszko PR, et al. Further neuroimaging evidence for the deficit subtype of schizophrenia: a cortical connectomics analysis. *JAMA Psychiatry*. 2015 May;72(5):446-55. doi: <http://dx.doi.org/10.1001/jamapsychiatry.2014.3020>. PMID: 25786193 **Not bipolar disorder**
917. Whiskey E, Taylor D. Pramipexole in unipolar and bipolar depression. *Psychiatric Bulletin*. 2004;28(12):438-40. doi: <http://dx.doi.org/10.1192/pb.28.12.438>. **Ineligible study design**
918. Wilcox J. Divalproex sodium in the treatment of aggressive behavior. *Annals of Clinical Psychiatry*. 1994 Mar;6(1):17-20. PMID: 7951640 **Bipolar not analyzed separately**
919. Williams JM, Alatiq Y, Crane C, et al. Mindfulness-based Cognitive Therapy (MBCT) in bipolar disorder: preliminary evaluation of immediate effects on between-episode functioning. *Journal of Affective Disorders*. 2008 Apr;107(1-3):275-9. PMID: 17884176 **Bipolar not analyzed separately**
920. Wilson KC, Scott M, Abou-Saleh M, et al. Long-term effects of cognitive-behavioural therapy and lithium therapy on depression in the elderly. *British Journal of Psychiatry*. 1995 Nov;167(5):653-8. PMID: 8564323 **Not bipolar disorder**
921. Wilting I, Heerdink ER, Mersch PP, et al. Association between lithium serum level, mood state, and patient-reported adverse drug reactions during long-term lithium treatment: a naturalistic follow-up study. *Bipolar Disorders*. 2009 Jun;11(4):434-40. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00699.x>. PMID: 19500096 **Bipolar not analyzed separately**
922. Winsberg ME, DeGolia SG, Strong CM, et al. Divalproex therapy in medication-naïve and mood-stabilizer-naïve bipolar II depression. *Journal of Affective Disorders*. 2001 Dec;67(1-3):207-12. PMID: 11869770 **Ineligible study design**
923. Woo YS, Bahk WM, Jon DI, et al. Rash in adult patients receiving lamotrigine to treat bipolar I disorder in Korea: a multicenter, prospective, naturalistic, open-label trial. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2009 Oct 1;33(7):1147-52. doi: <http://dx.doi.org/10.1016/j.pnpbp.2009.06.010>. PMID: 19540298 **Ineligible study design**
924. Woo YS, Shim IH, Wang HR, et al. A diagnosis of bipolar spectrum disorder predicts diagnostic conversion from unipolar depression to bipolar disorder: a 5-year retrospective study. *Journal of Affective Disorders*. 2015 Mar 15;174:83-8. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.034>. PMID: 25486276 **Ineligible study design**
925. Worthington MA, El-Mallakh RS. A naturalistic retrospective review of weight gain in bipolar patients treated with second generation antipsychotics. *Journal of Clinical Psychopharmacology*. 2015 Apr;35(2):192-3. doi: <http://dx.doi.org/10.1097/JCP.0000000000000271>. PMID: 2015-13623-015 **Ineligible study design**
926. Wu CS, Hsieh MH, Tang CH, et al. Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder. *Journal of Affective Disorders*. 2016 Jun;197:189-95. doi: <https://dx.doi.org/10.1016/j.jad.2016.03.043>. PMID: 26994437 **Ineligible study design**
927. Wu CS, Wang SC, Yeh IJ, et al. Comparative risk of seizure with use of first- And Second-Generation antipsychotics in patients with Schizophrenia and mood disorders. *Journal of Clinical Psychiatry*. 2016 May;77(5):e573-e9. doi: <http://dx.doi.org/10.4088/JCP.15m09898>. PMID: 610733712 **Ineligible intervention**

928. Wu F, Laber EB, Lipkovich IA, et al. Who will benefit from antidepressants in the acute treatment of bipolar depression? A reanalysis of the STEP-BD study by Sachs et al. 2007, using Q-learning. *International Journal of Bipolar Disorders*. 2015;3(1)doi: <http://dx.doi.org/10.1186/s40345-014-0018-5>. PMID: 2015897901 **No eligible outcomes reported**
929. Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biological Psychiatry*. 2009 Aug 1;66(3):298-301. doi: <http://dx.doi.org/10.1016/j.biopsych.2009.02.018>. PMID: 19358978 **Ineligible study design**
930. Xia G, Gajwani P, Muzina DJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. *International Journal of Neuropsychopharmacology*. 2008 Feb;11(1):119-30. PMID: 17335643 **Ineligible study design**
931. Xu AJ, Niciu MJ, Lundin NB, et al. Lithium and valproate levels do not correlate with ketamine's antidepressant efficacy in treatment-resistant bipolar depression. *Neural Plasticity*. 2015;2015(858251)doi: <http://dx.doi.org/10.1155/2015/858251>. PMID: 2015155220 **Ineligible study design**
932. Yaroslavsky Y, Grisaru N, Chudakov B, et al. Is TMS therapeutic in mania as well as in depression? *Electroencephalography & Clinical Neurophysiology - Supplement*. 1999;51:299-303. PMID: 10590963 **Not bipolar disorder**
933. Yatham LN. Mood stabilization and the role of antipsychotics. *International Clinical Psychopharmacology*. 2002 Aug;17 Suppl 3:S21-7. PMID: 12570068 **Ineligible study design**
934. Yatham LN. A clinical review of aripiprazole in bipolar depression and maintenance therapy of bipolar disorder. *Journal of Affective Disorders*. 2011 Jan;128 Suppl 1:S21-8. doi: [http://dx.doi.org/10.1016/S0165-0327\(11\)70005-2](http://dx.doi.org/10.1016/S0165-0327(11)70005-2). PMID: 21220077 **Ineligible study design**
935. Yatham LN, Binder C, Riccardelli R, et al. Risperidone in acute and continuation treatment of mania. *Int Clin Psychopharmacol*. 2003 Jul;18(4):227-35. doi: 10.1097/01.yic.0000074990.54339.e3. PMID: 12817157 **Ineligible study design**
936. Yatham LN, Calabrese JR, Kusumakar V. Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options. *Bipolar Disorders*. 2003 Apr;5(2):85-97. PMID: 12680897 **Ineligible study design**
937. Yatham LN, Fountoulakis KN, Rahman Z, et al. Efficacy of aripiprazole versus placebo as adjuncts to lithium or valproate in relapse prevention of manic or mixed episodes in bipolar I patients stratified by index manic or mixed episode. *Journal of Affective Disorders*. 2013 May;147(1-3):365-72. doi: <http://dx.doi.org/10.1016/j.jad.2012.11.042>. PMID: 23290791 **Duplicate reference**
938. Yatham LN, Kusumakar V, Calabrese JR, et al. Third generation anticonvulsants in bipolar disorder: a review of efficacy and summary of clinical recommendations. *Journal of Clinical Psychiatry*. 2002 Apr;63(4):275-83. PMID: 12000201 **Ineligible study design**
939. Yatham LN, Vieta E, Goodwin GM, et al. Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *British Journal of Psychiatry*. 2016 Jan;208(1):78-86. doi: <http://dx.doi.org/10.1192/bjp.bp.114.147587>. PMID: 25999335 **Ineligible study design**

940. Ye BY, Jiang ZY, Li X, et al. Effectiveness of cognitive behavioral therapy in treating bipolar disorder: An updated meta-analysis with randomized controlled trials. *Psychiatry and Clinical Neurosciences*. 2016 01 Aug;70(8):351-61. doi: <http://dx.doi.org/10.1111/pcn.12399>. PMID: 611542365 **Ineligible study design**
941. Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011 Jan;36(2):375-89. doi: <http://dx.doi.org/10.1038/npp.2010.192>. PMID: 20980991 **Ineligible study design**
942. Yoldi-Negrete M, Flores-Ramos M, Rodriguez-Ramirez AM, et al. The use of quetiapine for comorbid bipolar and obsessive compulsive disorders. *Current Psychopharmacology*. 2015 01 Aug;4(2):103-11. PMID: 608569783 **Ineligible study design**
943. Young AH, Cookson J, Elliott B, et al. Managing the aftermath of mania - Newcastle, 2 September 2005: Consensus Meeting Statement. *Journal of Psychopharmacology*. 2006 Mar;20(2 Suppl):51-4. PMID: 16551673 **Ineligible study design**
944. Young AH, Gallagher P, Watson S, et al. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology*. 2004 Aug;29(8):1538-45. PMID: 15127079 **Ineligible study design**
945. Young AH, Geddes JR, Macritchie K, et al. Tiagabine in the maintenance treatment of bipolar disorders. *Cochrane Database of Systematic Reviews*. 2006(3):CD005173. PMID: 16856081 **Ineligible study design**
946. Young AH, Geddes JR, Macritchie K, et al. Tiagabine in the treatment of acute affective episodes in bipolar disorder: efficacy and acceptability. *Cochrane Database of Systematic Reviews*. 2006(3):CD004694. PMID: 16856056 **Ineligible study design**
947. Young AH, McElroy SL, Olausson B, et al. A randomised, placebo-controlled 52-week trial of continued quetiapine treatment in recently depressed patients with bipolar I and bipolar II disorder. *The World Journal of Biological Psychiatry*. 2014 2014;15(2):96-112. doi: <http://dx.doi.org/10.3109/15622975.2012.665177>. PMID: 22404704 **Ineligible study design**
948. Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. *American Journal of Psychiatry*. 2000 Jan;157(1):124-6. PMID: 10618026 **No eligible outcomes reported**
949. Young RC, Schulberg HC, Gildengers AG, et al. Conceptual and methodological issues in designing a randomized, controlled treatment trial for geriatric bipolar disorder: GERI-BD. *Bipolar Disorders*. 2010 Feb;12(1):56-67. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00779.x>. PMID: 20148867 **Ineligible study design**
950. Zarate CA, Jr. Antipsychotic drug side effect issues in bipolar manic patients. *Journal of Clinical Psychiatry*. 2000;61 Suppl 8:52-61; discussion 2-3. PMID: 10811244 **Ineligible study design**
951. Zarate CA, Jr., Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biological Psychiatry*. 2004 Jul 1;56(1):54-60. PMID: 15219473 **Ineligible study design**

952. Zarate CA, Jr., Singh JB, Carlson PJ, et al. Efficacy of a protein kinase C inhibitor (tamoxifen) in the treatment of acute mania: a pilot study.[Erratum appears in Bipolar Disord. 2007 Dec;9(8):932]. Bipolar Disorders. 2007 Sep;9(6):561-70. PMID: 17845270 **Fewer than 11 subjects per arm**
953. Zarate CA, Jr., Tohen M, Baldessarini RJ. Clozapine in severe mood disorders. Journal of Clinical Psychiatry. 1995 Sep;56(9):411-7. PMID: 7665540 **Ineligible study design**
954. Zaretsky AE, Rizvi S, Parikh SV. How well do psychosocial interventions work in bipolar disorder? [References]. The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie. 2007 2007;52(1):14-21. **Ineligible study design**
955. Zerjav-Lacombe S, Tabarsi E. Lamotrigine: a review of clinical studies in bipolar disorders. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie. 2001 May;46(4):328-33. PMID: 11387788 **Ineligible study design**
956. Zeschel E, Bingmann T, Bechdolf A, et al. Temperament and prodromal symptoms prior to first manic/hypomanic episodes: results from a pilot study. Journal of Affective Disorders. 2015 Mar 1;173:39-44. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.031>. PMID: 25462394 **Ineligible study design**
957. Zupancic ML. Role of atypical antipsychotics in rapid cycling bipolar disorder: a review of the literature. Annals of Clinical Psychiatry. 2011 May;23(2):141-9. PMID: 21547275 **Ineligible study design**

Appendix Table D1. Studies of antipsychotics excluded for withdrawal rates >50%

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Masand, 2008 ¹⁸⁸ 18668014	I: Aripiprazole C: Placebo	n=161; BD I	post hoc analysis of Keck, 2006 (J Clin Psychiatry 2006; 67: 626-637) ² analyzing remission criteria 26 week RCT of responders
Suppes, 2008 ⁸¹⁷ 17904226	I: Aripiprazole C: Placebo	n=534; BD I	post hoc pooled analysis of Sachs, 2007 (J. Psychopharmacol. 20, 536–546) ⁴ and Keck, 2003 (Am. J. Psychiatry 160, 1651–1658) by disease traits ³ 3 week RCT
Sachs, 2007 ⁷³³ 17915976	I: Aripiprazole C: Placebo	n=513; BD I	post hoc pooled analysis of Keck 2003 (Am J Psychiatry 2003; 160: 1651-1658) ⁵ and Sachs, 2007 (J Psychopharmacol 2006; 20: 536-546) ⁴ analyzed by agitation level 3 week RCT
Keck, 2007 ⁴⁵⁵ 17960961	I: Aripiprazole C: Placebo	n=66; BD I	extension of included 26 week RCT in Keck, 2006 (J Clin Psychiatry 2006; 67:626-637) ²
Keck, 2003 ⁴⁵⁷ 12944341	I: Aripiprazole C: Placebo	n=262; BD I	3 week RCT
El Mallakh, 2010 ²⁵¹ 20728318	I: Aripiprazole (high dose) C1: Aripiprazole (low dose) C2: Placebo	n=401; BD I	3 week RCT
Keck, 2009 ⁴⁶⁶ 18835043	I: Aripiprazole C1: Lithium C2: Placebo	n=181; BD I	3 week RCT + 9 week extension of responders
El-Mallakh, 2012 ²⁵⁷ 22209190	I: Aripiprazole C1: Lithium C2: Placebo	n=99; BD I	40 week extension of excluded 12 week study in Keck, 2009 (J Aff Disorders 112 (1–3), 36–49)
Moreno, 2007 ⁶¹⁰ 17334533	I: Haloperidol C: Olanzapine	n=12; BD I	6 week RCT; sleep study
Tohen, 2009 ⁸⁵⁵ 19054570	I: Olanzapine C: Placebo	n=121; BD I	Subgroup analysis of Tohen 2006 ¹²
Vieta, 2004 ⁸⁶⁶ 15491248 15641874 ³⁹⁷	I: Olanzapine C: Placebo	n=254 RCT; n=113 extension ; BD I	post hoc pooled analysis of Tohen, 1999 (Am J Psychiatry 156:702-709) ¹⁴ and Tohen, 2000 (Arch gen Psychiatry 57:841-849) comparing rapid and non-rapid cyclers. Year-long extension not cited and could not be located. 3-4 week RCT + 1 year extension (maintenance)
Baker, 2003 ³⁸ 12640214	I: Olanzapine C: Placebo	n=68; BD I with severe dysphoric mania	3 week RCT pooling of Tohen, 1999 (Am. J Psychiatry 156 (5), 702-709) ¹⁴ and Tohen, 2000 (Arch. General Psychiatry 57 (9), 841–849)

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Baker, 2003 ³⁷ 12507747	I: Olanzapine C: Placebo	n=254; BD I	3 week RCT pooling of Tohen, 1999 (Am. J Psychiatry 156 (5), 702-709) ¹⁴ and Tohen, 2000 (Arch. General Psychiatry 57 (9), 841-849)
Baldessarini, 2003 ⁴² 12920413	I: Olanzapine C: Placebo	n=254; BD I	3-4 weeks RCT pooling of Tohen, 1999 (Am. J Psychiatry 156 (5), 702-709) ¹⁴ and Tohen, 2000 (Arch. General Psychiatry 57 (9), 841-849)
Chengappa, 2003 ¹⁶¹ 12656931	I: Olanzapine C: Placebo	n=246; BD I	3 week RCT pooling of Tohen, 1999 (Am. J Psychiatry 156 (5), 702-709) ¹⁴ and Tohen, 2000 (Arch. General Psychiatry 57 (9), 841-849) with revised definitions for response and remission)
Tohen, 1999 ⁸⁵³ 10327902	I: Olanzapine C: Placebo	n=139; BD I	3 week RCT
Ketter, 2006 ⁴⁸⁰ 16426094	I: Olanzapine C: Lithium	n=431; BD I	post hoc analysis of Tohen, 2005 (Am J Psychiatry 2005; 162: 1281-1290) by number of previous mood episodes 12 months RCT
Suppes, 2005 ⁸¹⁶ 16253344	I: Olanzapine C: Valproate	n=251; BD I	Post hoc analysis of Tohen, 2003 (Am. J. Psychiatry 160, 1272-1276) ²¹ concerning rapid cycling 47 week RCT (maintenance)
Novick, 2010 ⁶⁴⁵ 20531011 modelled after Perlis, 2006 (J Clin Psychiatry 67: 1747- 1753)	I: Olanzapine C: Risperidone	n=245; BD I	12 week acute observational +2 year observational
Suppes, 2013 ⁸¹⁹ 23521871	I: Quetiapine C: Placebo	n=81; BD II	8 week RCT
Nejtek, 2008 ⁶²⁷ 18681757	I: Quetiapine C: Risperidone	n=96; BD I or II	20 week RCT; stimulant users
Hirschfeld, 2004 ⁴⁰⁵ 15169694	I: Risperidone C: Placebo	n=262; BD I	3 week RCT
Sanger, 2003 ⁷⁵³ 12507748	I: Olanzapine C: Placebo	N=45 BD I; rapid cycling	3 week RCT
Stahl, 2010 ⁸⁰⁹ 19616304	I: Ziprasidone C: Placebo	n=181; BD I	post hoc pooled analysis of Keck, 2003 (Am. J. Psychiatry 160, 741-748) and Potkin, 2005 (J. Clin. Psychopharmacol. 25, 301-310) in dysphoric mania 3 week RCT
Vieta, 2010 ⁸⁹³ 19074536	I: Ziprasidone C1: Haloperidol C2: Placebo	n=438; BD I	3 week 3 arm RCT + 9 week 2 arm extension of responders

Abbreviations: BP=bipolar disorder; C=comparison; I=intervention; NS=not significant; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table D2. Studies of antipsychotics + mood stabilizers or antidepressants excluded for withdrawal rates >50%

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Chou, 1999 ¹⁶⁵ 10587284	I: Haloperidol (high or low dose) + Lithium C: Haloperidol (high or low dose) + Lorazepam	n=63; BD I	3 week RCT
Katagiri, 2012 ⁴⁴⁸ 22356118 extension of 6 week RCT (not cited, unable to locate)	I: Olanzapine + Lithium C1: Olanzapine + Valproate C2: Olanzapine	n=139; BD I	18 week observational (maintenance)
Brown, 2009 ¹¹⁹ 19079815 Continuation of Brown, 2006 (J Clin Psychiatry 60, 79-88)	I: Olanzapine + Fluoxetine (antidepressant) C: Lamotrigine	n=410; BD I	25 week RCT depression (not proper time-to-event and post-hoc)
Vieta, 2012 ⁸⁹⁴ 23062763	I: Quetiapine + Lithium OR Valproate C: Placebo + Lithium OR Valproate	n=445; BD I	post hoc pooled analysis of Suppes, 2009 (Am J Psychiatry 166, 476–488) and Vieta, 2008 (J Aff Disorders 109, 251–263) of those with mixed episodes 104 week RCT (maintenance)

Abbreviations: BP=bipolar disorder; C=comparison; I=intervention; NS=not significant; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table D3. Studies of mood stabilizers excluded for withdrawal rates >50%

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Weisler, 2008 ⁹⁰⁹ 22778707	I: Carbamazepine ER (once-daily) C: Carbamazepine ER (twice-daily)	n=111; BD I	12 week RCT
Weisler, 2004 ⁹¹⁰ 15119909	I: Carbamazepine ER C: Placebo	n=204; BD I	3 week RCT
El-Mallakh, 2009 ²⁵⁹ 19367153	I: Carbamazepine ER C: Carbamazepine	n=41; BD I or II	3 month RCT
Licht, 2010 ⁵²⁷ 20712749	I: Lamotrigine C: Lithium	n=155; BD I	6 month RCT
Suppes, 2008 ⁸²⁰ 18358540	I: Lamotrigine C: Lithium	n=102; BD II	16 week RCT
Bowden, 2006 ¹⁰⁸ 16816224	I: Lamotrigine C1: Lithium	n=254; BD I, obese vs. non-obese	pools two studies from Goodwin, 2004 (J Clin Psychiatry (65) 432-441) 18 month RCT (maintenance)

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Wang, 2010 ⁹⁰⁴ 21240149	I: Lamotrigine + Lithium AND Valproate C: Placebo + Lithium AND Valproate	n=36; BD I or II	12 week RCT; substance users with recent depression and rapid cycling
Bowden, 2012 ¹¹⁴ 22708645	I: Lamotrigine + Valproate C: Lamotrigine	n=164 (treatment); n=86 (randomized); BD I or II	8 week treatment + 8 month RCT of responders (maintenance)
Goldberg, 2009 ³⁵⁴ 19689918 pooled post hoc analysis of Bowden, 2003 (Arch Gen Psych 2003; 60: 392-400) and Calabrese, 2003 (J Clin Psych 2003; 64: 1013- 1024)	I: Lamotrigine C1: Lithium C2: Placebo	n=966 observational; n=463 RCT ; BD I	8-16 week observational treatment phase with Lamotrigine + 18 month RCT (maintenance)
Solomon, 1996 ⁸⁰³ 8831438	I: Lithium , High Dose C: Lithium, Low Dose	n=94; BD I	≥2 year RCT (maintenance)
Small, 1995 ⁷⁹⁴ 7491378	I: Lithium + Carbamazepine C: Lithium + Haloperidol	n=33; BD I	8 week RCT
Kakkar, 2009 ⁴⁴⁴ 19324530	I: Oxcarbazepine C: Valproate	n=60; BD I	12 week RCT
Bowden, 1994 ¹⁰⁷ 8120960	I: Valproate C1: Lithium C2: Placebo	n=179; BD I	3 week RCT
Hirschfeld, 2010 ⁴⁰³ 20361904	I: Divalproex C: Placebo	n=225; BD I	3 week RCT
McElroy, 2010 ⁵⁷⁰ 20361901	I: Divalproex C: Placebo	n=62; BD I, II or NOS	8 week RCT
Oquendo, 2011 ⁶⁵⁴ 21768611	I: Valproate + Various Adjuncts C: Lithium + Various Adjunct	n=98; BD I, II, or NOS	2.5 year RCT; study of suicide
Salloum, 2005 ⁷⁴⁶ 15630071	I: Valproate + Lithium + Dual diagnosis recovery counseling C1: Lithium + Dual diagnosis recovery counseling	n=59; BD I	24 week RCT; alcoholism (maintenance)

Abbreviations: BP=bipolar disorder; C=comparison; I=intervention; NS=not significant; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table D4. Studies of other drugs excluded for withdrawal rates >50%

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Ghaemi, 2010 ³⁴² 20409444 2015371706 ⁹⁰⁰	I: Antidepressant + Mood Stabilizer C: Mood Stabilizer	n=70; BD NR	3 year RCT; antidepressant discontinuation study
Geddes, 2016 ³³¹ 26687300	I: Lamotrigine + Quetiapine C: Placebo + Quetiapine	n=202; BD I or II	12 week RCT
Gonzalez Arnold, 2015 ³⁵⁹ 25827507	I: Optimized Personal Treatment (OPT) + Lithium C1: OPT	n = 283; BD I or II	6 month RCT; racial disparity study
Vik, 2013 ⁸⁹⁵ 23551803	I: Calcitonin + Mood Stabilizer And/Or Antipsychotic C: Placebo + Mood Stabilizer And/Or Antipsychotic	n=46; BD I	3 week RCT
Mishory, 2003 ⁶⁰⁰ 14636372	I: Phenytoin C: Placebo	n=23; BD I	6 month observational crossover
Grunze, 2015 ³⁸² 25484179	I: Eslicarbazepine acetate (various dose arms) C: Placebo	n= 200 placebo controlled RCT; n=87 dose RCT; BD I	3 week placebo controlled RCT + 6 month RCT of responders without placebo control for dose effects
Amsterdam, 1998 ¹⁶ 9864074	I: Fluoxetine C: Placebo	n=89, 12 week n=28, 50 week extension; BDII vs. unipolar;	12 week observational treatment phase + 50 week RCT of remitters
Amsterdam, 2013 ¹⁸ 23099447	I: Fluoxetine C1: Lithium C2: Placebo	n=81; BD II	post hoc analysis of Amsterdam, 2010 (Am J Psychiatry 2010; 167: 792–800) comparing rapid and non-rapid cycling patients

Abbreviations: BP=bipolar disorder; C=comparison; I=intervention; NS=not significant; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table D5. Studies of psychosocial therapy excluded for withdrawal rates >50%

Author, Year PMID	Intervention/ Comparison	N; BD Type	Study Description
Cardoso Tde, 2010 ¹⁴² , 213, 214 26348588 25300245 2015431675	I: Psychoeducationon biological rhythm C: Treatment as usual	n=61; BD	6 month RCT in young adults 18-29
Crowe, 2012 ²⁰⁴ 22070452	I: Nurse-led supportive care C: Usual care	n=36; BD	9 month RCT adults 18+
Lauder, 2015 ⁵¹¹ 25282145	I: Website-based interactive program MoodSwings-Plus C: Website-based program MoodSwings	n=156; BD I or II	12 month RCT

Abbreviations: BP=bipolar disorder; C=comparison; I=intervention; NS=not significant; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix E. Antipsychotics for Mania

Section 1. Aripiprazole for Acute Mania

Appendix Table E1. Characteristics of eligible studies: aripiprazole for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kanba, 20141 RCT Multisite Asia Industry RoB High 22540407	N = 258 Mean Age 38 Female 59% Japanese 32% Korean/Chinese 43% Other 25% BP-I 100% Inpatient	Manic/Mixed episode; YMRS ≥ 20 ; Current episode <4 weeks First Manic Episode Schizoaffective Neurological Disorders Other Mental Health Substance Abuse Pregnant/Nursing	Aripiprazole 24 mg/day (22.9 mg/day)	Placebo	3 weeks	YMRS CGI-BP-S Response Adverse Events Withdrawal 47%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Young, 20092 RCT Multisite All Continents Industry RoB Moderate 19118324	N = 332 Mean Age 41 Female 57% White 78% BP-I 100% Inpatient (weeks 1-2) Outpatient (weeks 3-12)	Manic/Mixed in acute relapse; YMRS ≥ 20 and MADRS ≤ 17 at baseline, < 25% decrease in YMRS score and ≤ 4 point MADRS score between screening and baseline visits; Current episode < 3 weeks First Manic Episode Schizoaffective Neurological Disorders Other Mental Health Taking Other Meds Substance Abuse	Aripiprazole 15-30 mg/day (22.0 mg/day)	C1: Placebo C2: Haloperidol 5-15 mg/day (7.4 mg/day)	12 weeks for aripiprazole and haloperidol; 3 weeks for placebo	YMRS CGI-BP-S Response Adverse Events EPS Withdrawal 27% at 3 weeks

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Sachs, 20063 RCT Multisite North America Industry RoB High 16401666	N = 272 Mean Age 39 Female 51% White 72% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3)	Manic/Mixed episode; YMRS ≥ 20; Current episode < 4 weeks First Manic Episode Schizoaffective Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Aripiprazole 15-30 mg/day (27.7 mg/day)	Placebo	3 weeks	YMRS CGI-BP-S Response Adverse Events EPS Withdrawal 47%
Vieta, 20054 RCT Multisite Not Disclosed Industry RoB Moderate 16135860	N = 347 Mean Age 42 Female 28% Race NR BP-I 100% Inpatient or Outpatient	Manic/Mixed; YMRS ≥ 20; Current episode < 4 weeks Other Mental Health Taking Other Meds Substance Abuse	Aripiprazole 15-30 mg/day	C1: Placebo C2: Haloperidol 10-15 mg/day	3 weeks (with withdrawal < 50%; 12 weeks total)	YMRS CGI-BP-S Response Adverse Events EPS Withdrawal 34%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; EPRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not

otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trials; YMRS = Young Mania Rating Scale

Appendix Table E2. Summary risk of bias assessments: aripiprazole for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Aripiprazole	Kanba, 2014 ¹ Industry 22540407	High	High dropout rate (47% overall); Randomization and blinding procedures not disclosed.
	Young, 2009 ² Industry 19118324	High	Moderate dropout rate (28%); Randomization and blinding procedures not disclosed.
	Sachs, 2006 ⁵ Industry 16401666	High	High withdrawal rate (47%), randomization and blinding procedures not disclosed
	Vieta, 2005 ⁶ Industry 16135860	Moderate	Blinding not described, moderate dropout level (34%), not balanced between the groups. Groups may not be comparable at time of analysis.

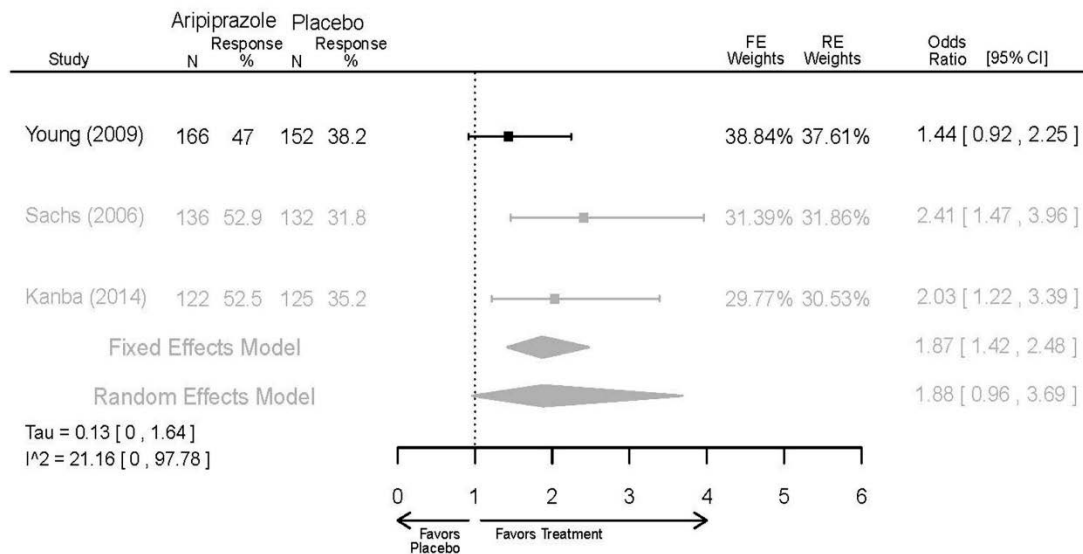
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Aripirazole Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

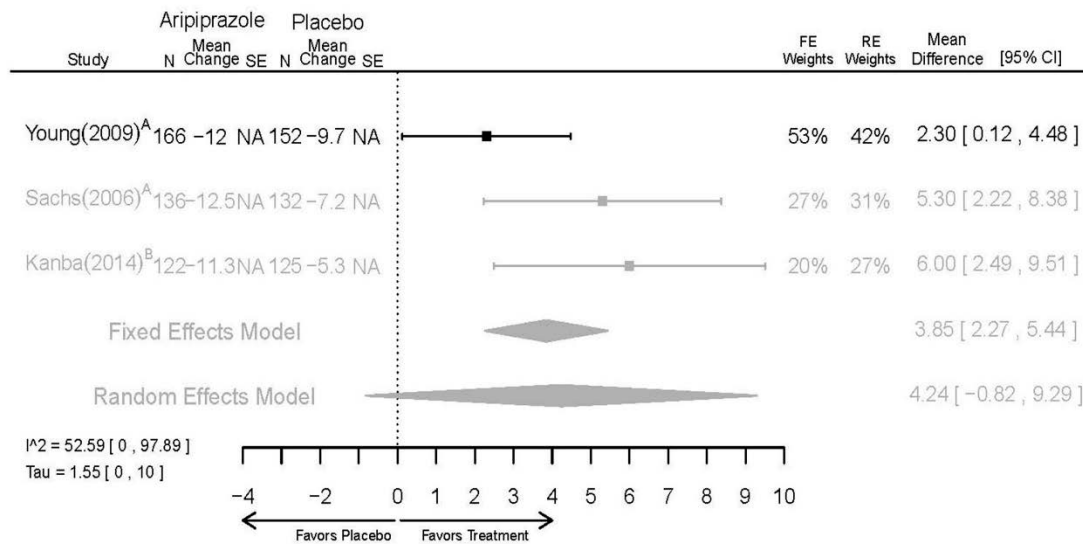
Appendix Figure E1. Aripiprazole vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



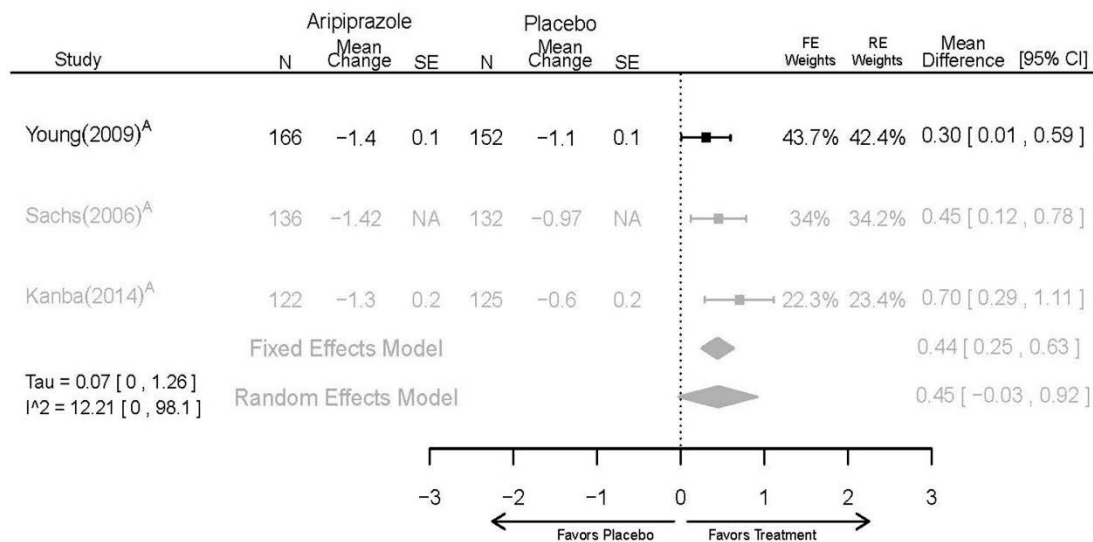
Appendix Figure E2. Aripiprazole vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to 3 Weeks



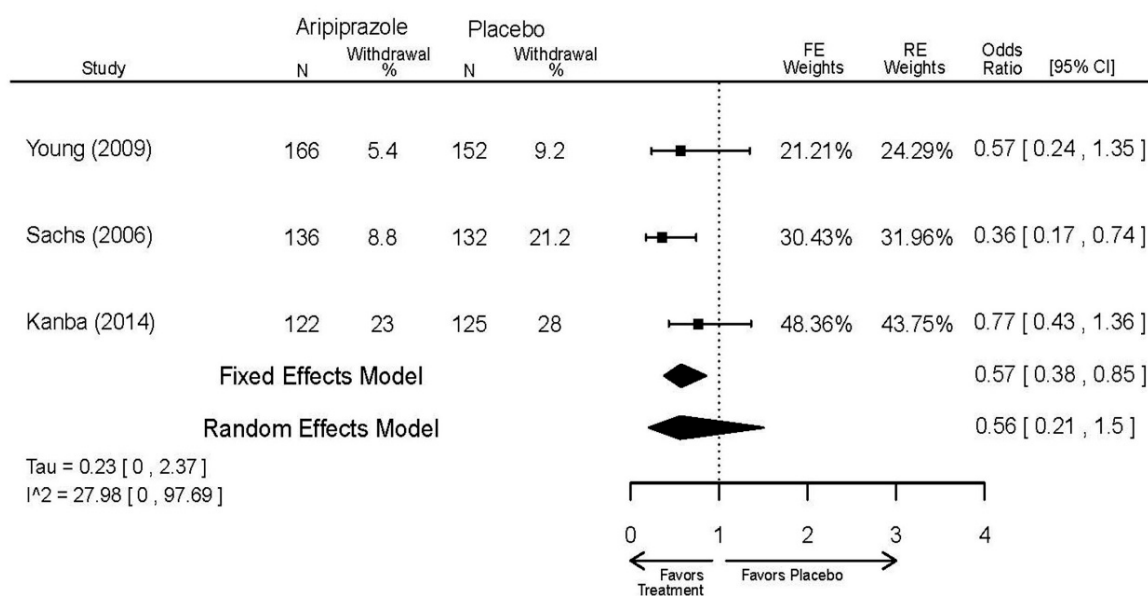
Appendix Figure E3. Aripiprazole vs. placebo – CGI-BP-S

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks



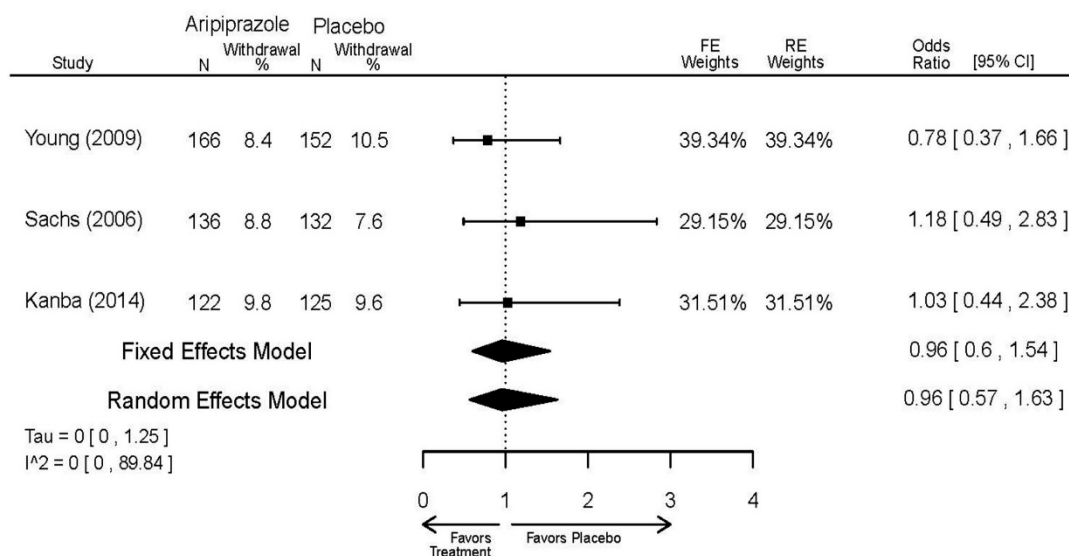
Appendix Figure E4. Aripiprazole vs. placebo – withdrawal lack of efficacy

Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



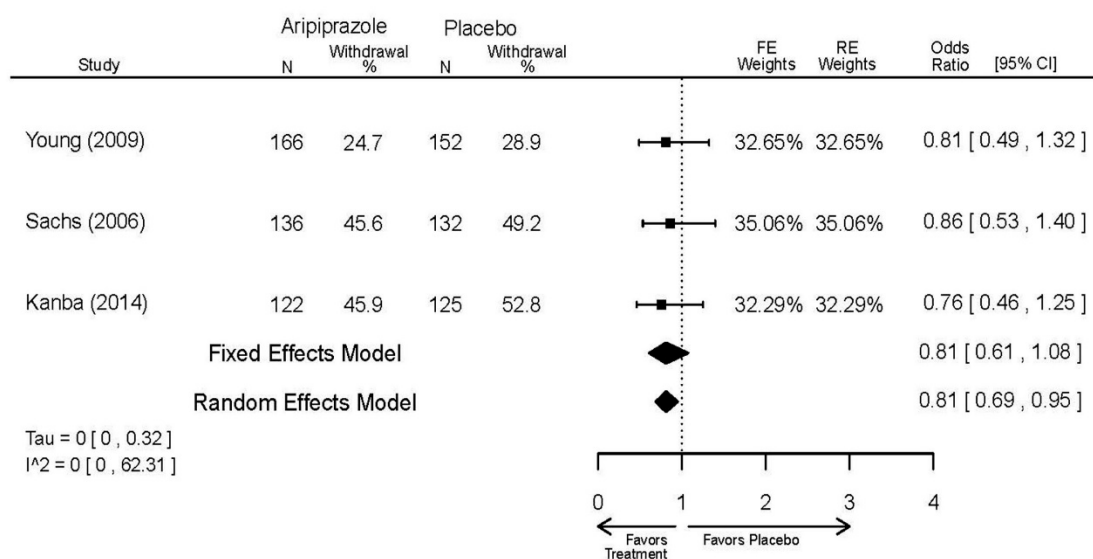
Appendix Figure E5. Aripiprazole vs. placebo – withdrawal adverse events

Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



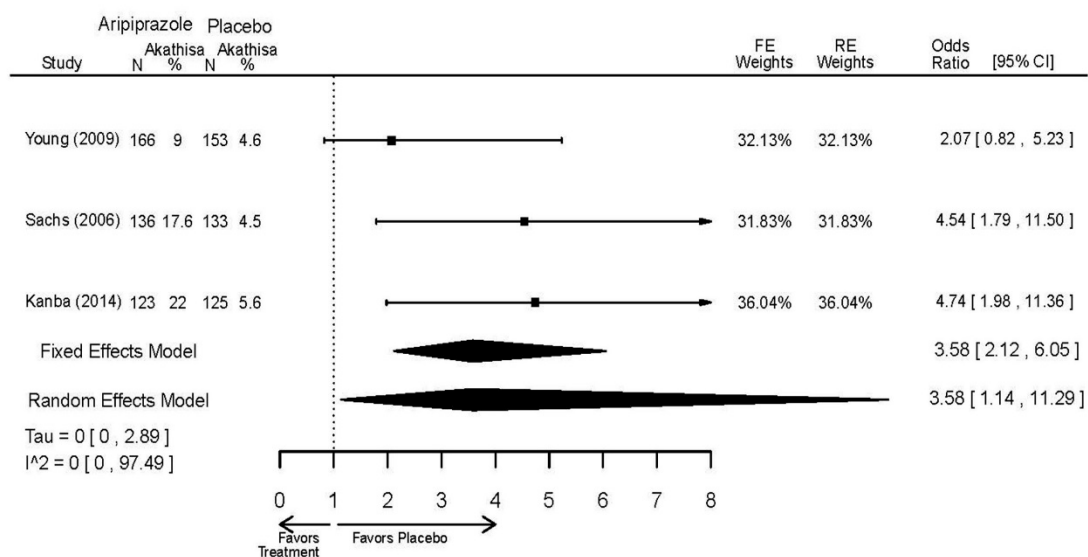
Appendix Figure E6. Aripiprazole vs. placebo – overall withdrawal

Odds Ratio of Overall Withdrawal

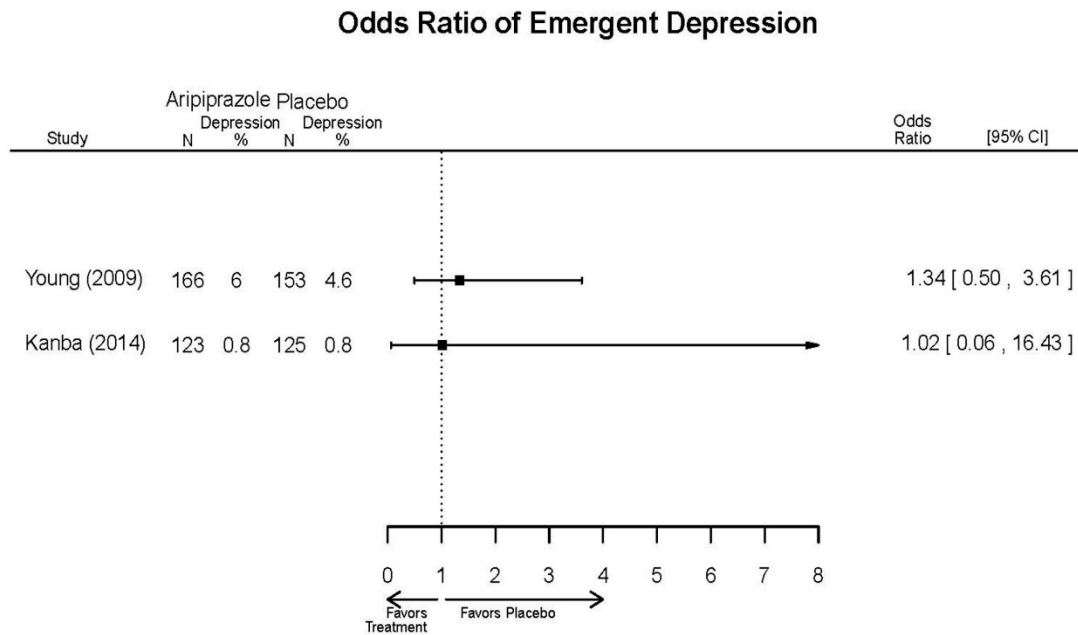


Appendix Figure E7. Aripiprazole vs. placebo – harms - akathisia

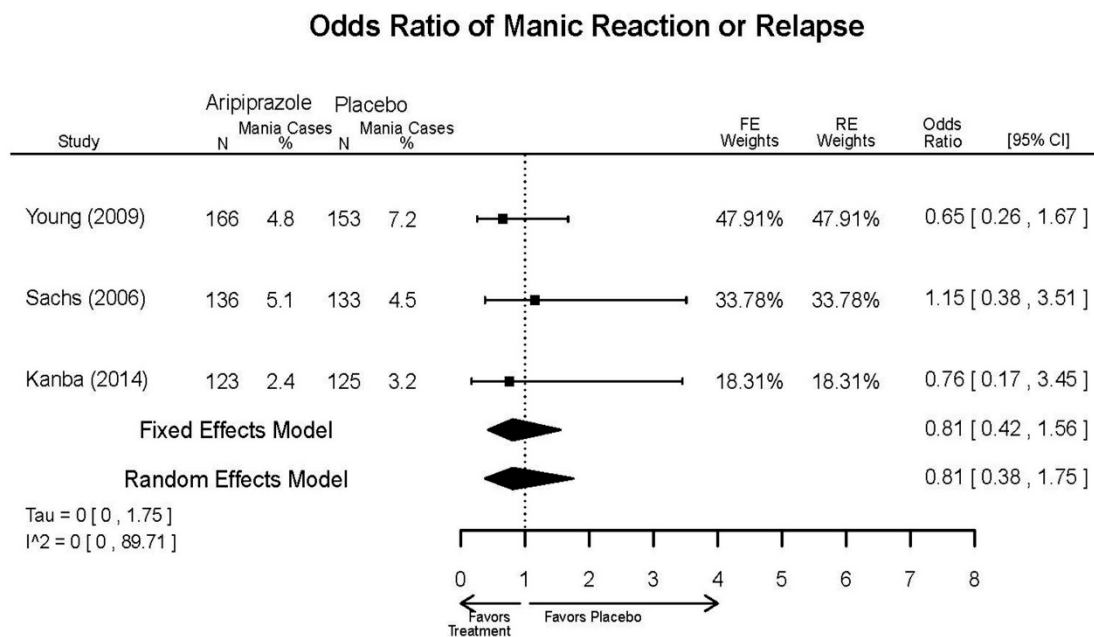
Odds Ratio of Akathisia



Appendix Figure E8. Aripiprazole vs. placebo – harms – emergent depression

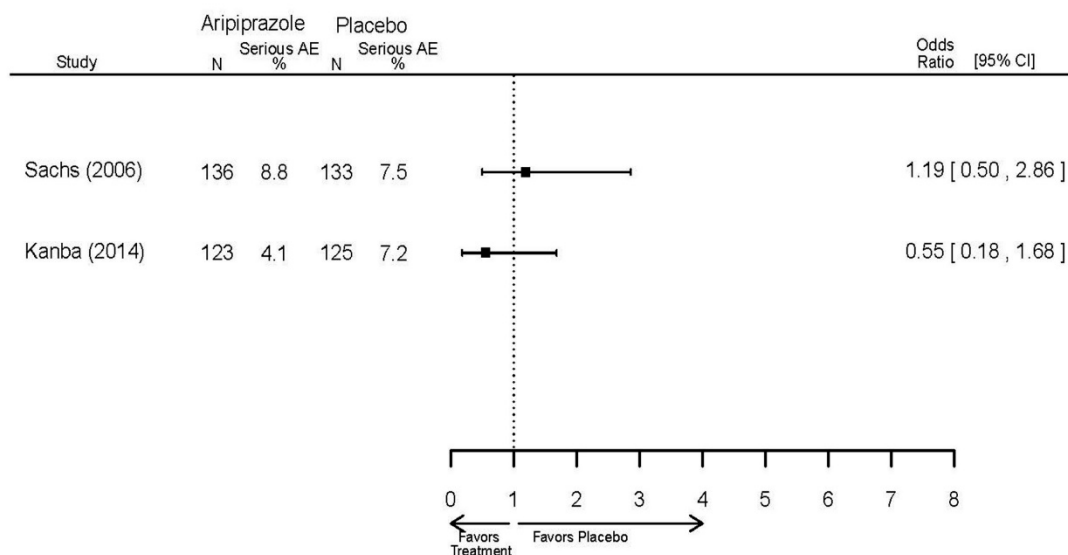


Appendix Figure E9. Aripiprazole vs. placebo – harms – emergent manic episode



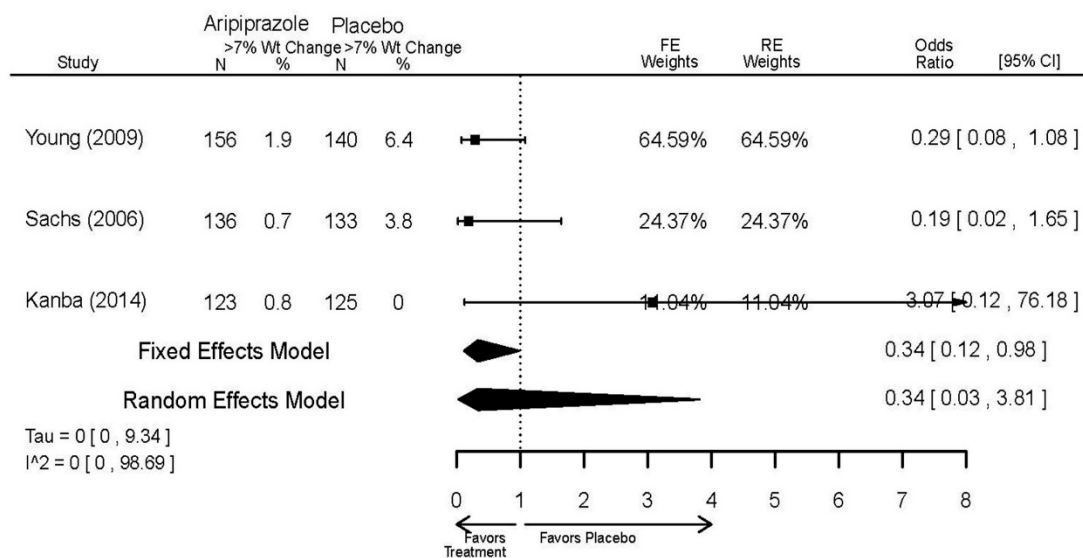
Appendix Figure E10. Aripiprazole vs. placebo – harms – serious adverse event

Odds Ratio of Experiencing a Serious Adverse Event Within 3 Weeks

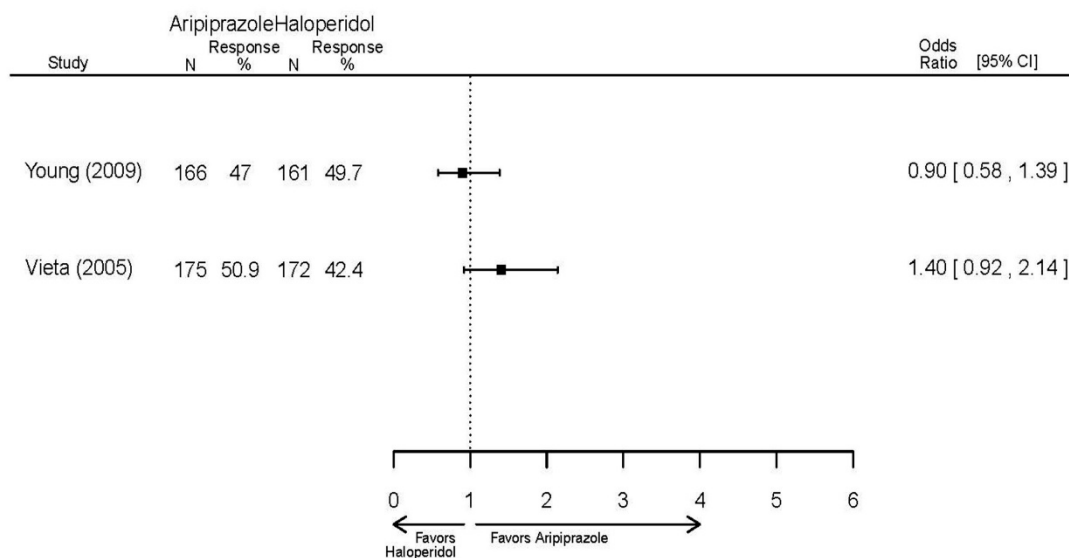


Appendix Figure E11. Aripiprazole vs. placebo – harms – weight gain

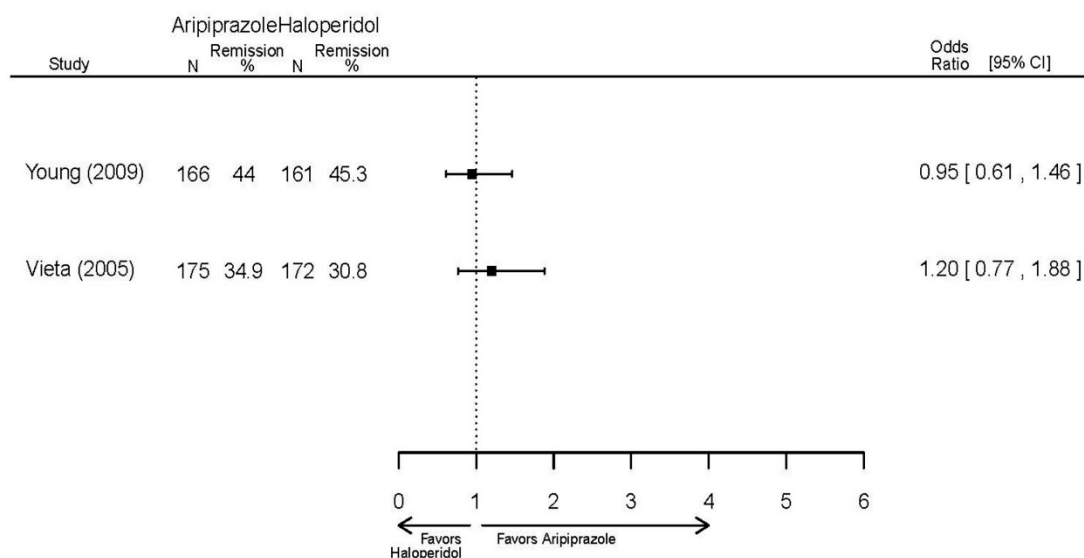
Odds Ratio of a >7% increase in weight



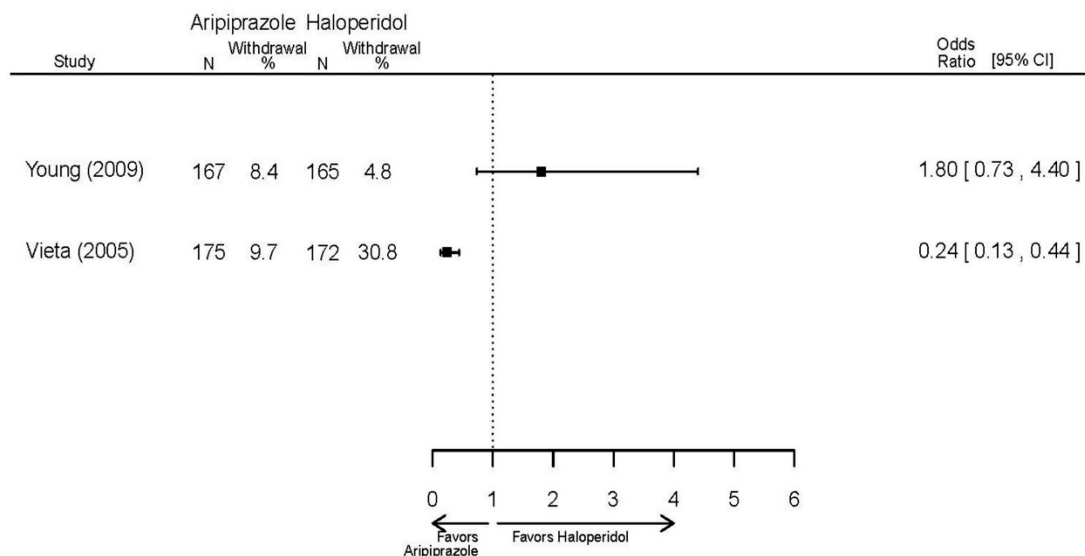
Appendix Figure E12. Aripiprazole vs. haloperidol – response
Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



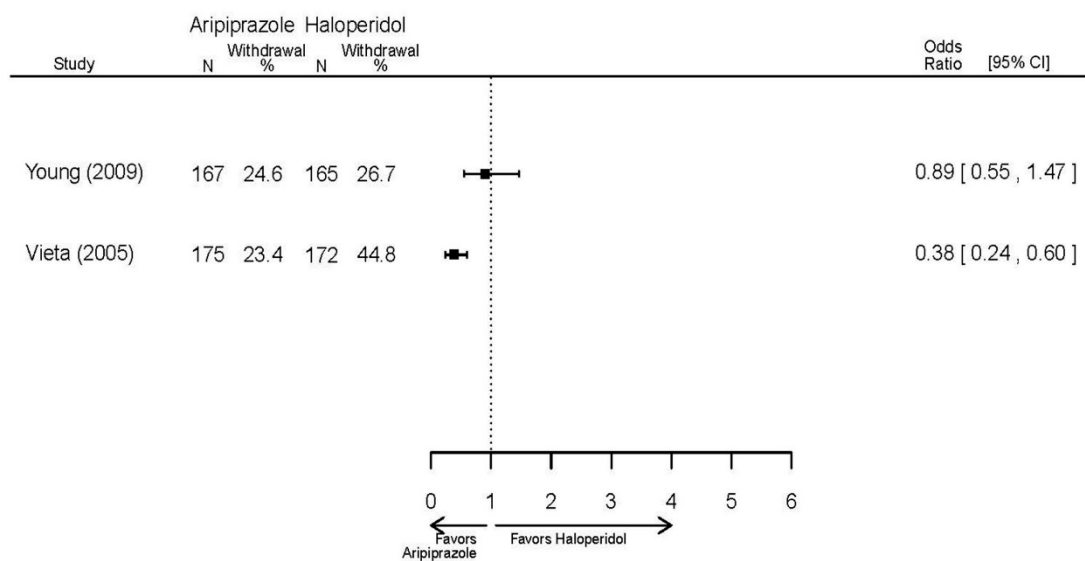
Appendix Figure E13. Aripiprazole vs. haloperidol – remission
Odds Ratio of Remission (YMRS drops to at least 12) at 3 Weeks



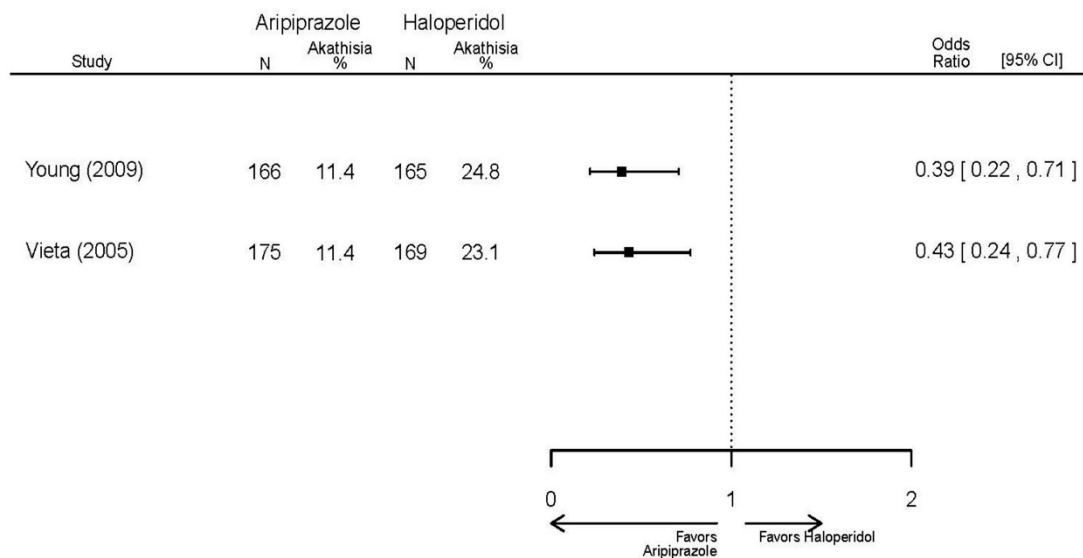
Appendix Figure E14. Aripiprazole vs. haloperidol – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at Week 3



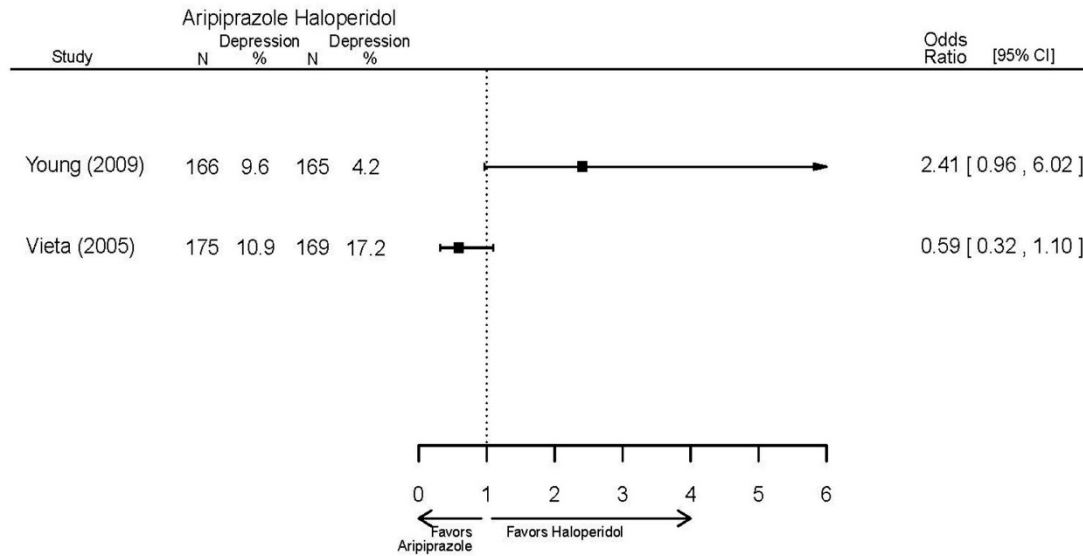
Appendix Figure E15. Aripiprazole vs. haloperidol – withdrawal – overall
Odds Ratio of Withdrawal due to All Causes at Week 3



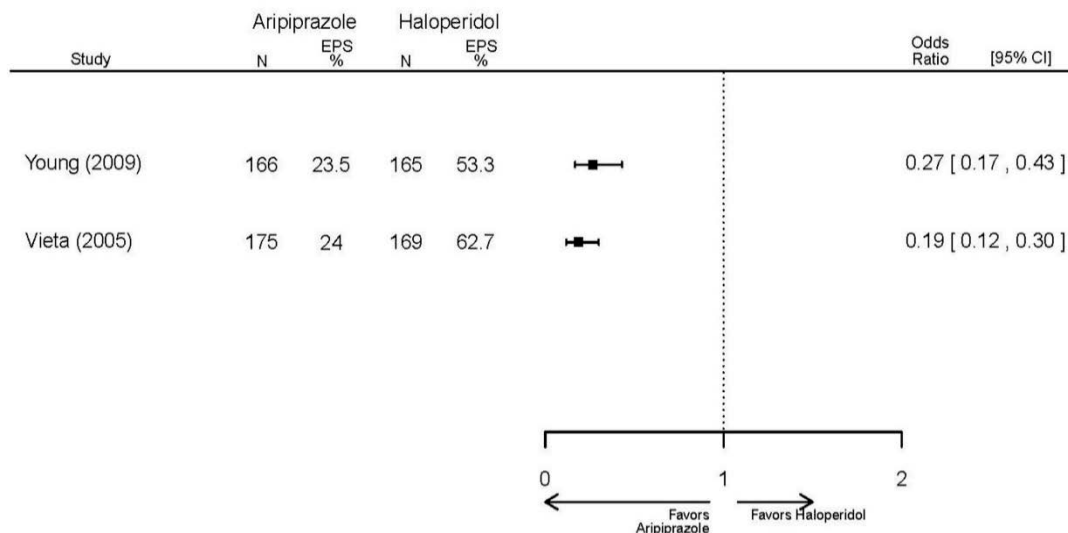
Appendix Figure E16. Aripiprazole vs. haloperidol – harms – akathisia
Odds Ratio of Akathisia



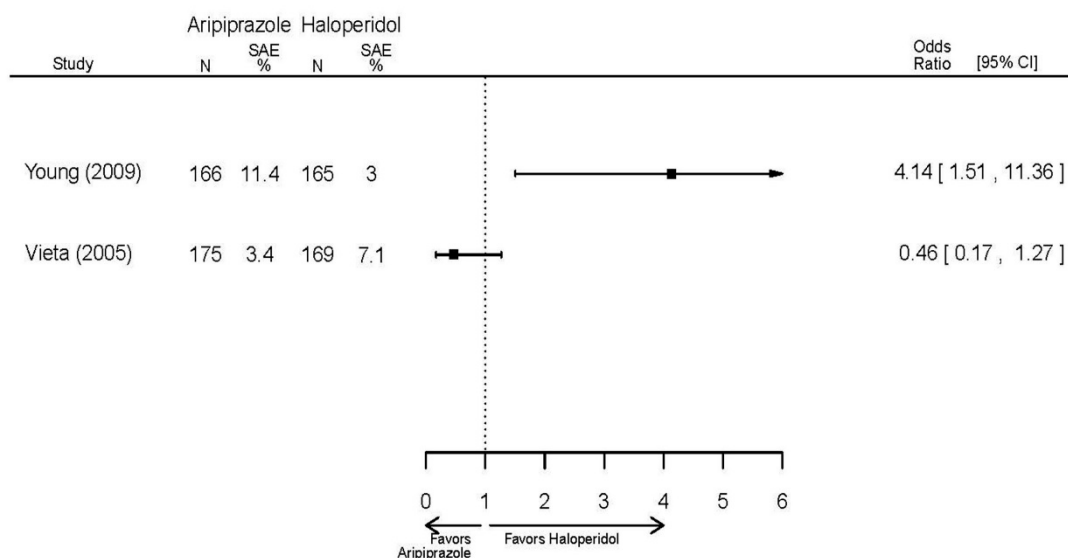
Appendix Figure E17. Aripiprazole vs. haloperidol – harms – emergent depression
Odds Ratio of Emergent Depression



Appendix Figure E18. Aripiprazole vs. haloperidol – harms – extrapyramidal symptoms
Odds Ratio of Extrapyramidal Symptoms



Appendix Figure E19. Aripiprazole vs. haloperidol – harms – serious adverse events
Odds Ratio of Serious Adverse Events at Last Measurement



Appendix Table E3. Outcomes summary: aripiprazole versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Aripiprazole	Kanba, 2014 ¹ 22540407 Moderate	See forest plot E1 above for Response.	See forest plot E2 above for YMRS.	NR	See forest plots E4, E5, E6 above for Withdrawals.	See forest plots E7, E8, E9, E10, E11 above for Adverse Effects. <u>Very Serious AE</u> 3 weeks 1 death during trial, unrelated to study medication
	Young, 2009 ² 19118324 Moderate	<u>Remission</u> 3 weeks NS Aripiprazole = 73/166 Placebo=56/152 OR = 1.35 (95% CI 0.86, 2.11) p 0.20	See forest plot E2 above for YMRS.	NR	See forest plots E4, E5, E6 above for Withdrawals.	See forest plots E7, E8, E9, E10, E11 above for Adverse Effects. <u>Very Serious AE</u> 3 weeks 1 non-fatal suicide attempt, unclear which study arm <u>SAE</u> 3 weeks Aripiprazole=19/166 Placebo=NR No statistical test reported <u>Extrapyramidal Symptoms</u> 3 weeks Aripiprazole=39/166 Placebo=NR No statistical test reported
	Sachs, 2006 ⁵ 16401666 Moderate	See forest plot E1 above for response.	See forest plot E2 above for YMRS.	NR	See forest plots E4, E5, E6 above for Withdrawals.	See forest plots E7, E8, E9, E10, E11 above for Adverse Effects.

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E4. Strength of evidence assessment: aripiprazole versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Aripiprazole vs. placebo	Response 3 wks YMRS 3 wks CGI-BP-S 3 wks Overall withdrawal Withdrawal lack of efficacy Withdrawal adverse events	3 RCT (n=823)	See forest plots	High	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E5. Outcomes summary: aripiprazole versus active comparator for acute mania

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Aripiprazole (15 or 30 mg/day) vs.. Haliperidol (5-15 mg/day)	Young, 2009 ² 19118324 Moderate High (12 weeks)	See forest plot above.	<p><u>YMRS, Mean Change</u> 3 weeks NS Aripiprazole =-12.0 Haloperidol =-12.8 No statistical test reported</p> <p>12 weeks NS Aripiprazole =-17.2 Haloperidol =-17.8 No statistical test reported</p> <p><u>CGI-BP-Sev, Mean Change</u> 3 weeks NS Aripiprazole =-1.4 Haloperidol =-1.5 No statistical test reported</p> <p>12 weeks NS Aripiprazole =-2.1 Haloperidol =-2.2 No statistical test reported</p>	NR	<p><u>Overall Withdrawal</u> 12 weeks NS Aripiprazole=72/167 Haloperidol=70/165 OR = 1.03 (95% CI 0.67, 1.59) ; P = 0.90</p> <p><u>Withdrawal Due to Lack of Efficacy</u> 3 weeks NS Aripiprazole=9/167 Haloperidol=10/165 OR = 0.88 (95% CI 0.35, 2.23) p= 0.79</p> <p>12 weeks NS Aripiprazole=13/167 Haloperidol=11/165 OR = 1.18 (.51, 2.72) ; P = .694</p> <p><u>Withdrawal Due to AEs</u> 12 weeks NS Aripiprazole=24/167 Haloperidol=18/165 OR=1.37 (.71, 2.63) ; P = 0.34</p>	<p><u>Very Serious AEs</u> 12 weeks 1 patient in haloperidol group suffered liver damage, potentially attributable to haloperidol</p> <p><u>Normalized Weight Change (>7% change)</u> 12 weeks NS Aripiprazole= 5.1% Haloperidol= 5.8% OR = 0.87 No statistical test reported</p> <p><u>Cases of Depression</u> 3 weeks Favors Comparator Aripiprazole= 10/166 Haloperidol= 3/165 OR = 3.33 (0.98, 15.83) ; P = 0.049</p> <p><u>Cases of Manic Reaction or Relapse at Last Measurement</u> 12 weeks Favors Comparator Aripiprazole= 8/166 Haloperidol= 1/165 OR = 7.36 (1.30, 186.76) ; P = 0.037</p>

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Vieta, 2005 ⁶ 16135860 Moderate	See forest plot above.	<u>YMRS</u> 3 weeks NS Aripiprazole -15.7 Haloperidol =-15.7 No statistical test reported <u>CGI-BP-Sev</u> 3 weeks NS Aripiprazole -2.0 Haloperidol =-1.9 No statistical test reported	NR	See forest plot above.	See forest plot above.

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; NS=not significant; OR=Odds Ratio; YMRS = Young Mania Rating Scale

Appendix Table E6. Strength of evidence assessment: aripiprazole versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Aripiprazole vs. haloperidol	Response 3 wk Remission 3 wk YMRS 3 wk Withdrawal	2 RCTs (n=674)	See table above	High	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 2. Asenapine for Acute Mania

Appendix Table E7. Characteristics of eligible studies: asenapine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Landbloom, 2016 ⁷ RCT Multisite 3 Continents Industry RoB Moderate 26496015	N = 367 Mean Age 44 Female 55% Race NR BP-I 100% Inpatient (week 1) Outpatient (weeks 2-3)	Mania; Structured clinical interview (MINI). Episode began at least 1 month prior to screening. YMRS ≥ 20 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions	Asenapine T1: 5 mg BID T2: 10mg BID	Placebo	3 weeks	Response (50% change YMRS scores) Remission (YMRS) YMRS CGI-BP-S PANSS MADRS SAEs EPS Withdrawal 28%
McIntyre, 2010 ⁸ RCT Multisite 3 Continents Industry RoB High 20096936	N = 488 Mean Age 39 Female 47% White 55% BP-I 100% Inpatient (week 1) Outpatient (weeks 2-3, subject to investigator discretion and successful passing of InterSePT Scale for Suicidal Thinking criteria)	Manic/Mixed; YMRS ≥ 20; Current episode ≤ 3 months First Manic Episode Neurological Disorders Substance Abuse Other Mental Health Taking Other Meds Lab/Other Conditions	Asenapine 10-20 mg/day (18.4 mg/day average) N=185	C1: Placebo n=98 C2: Olanzapine 5-20 mg/day n=205	3 weeks	CGI-BP-S MADRS Remission (YMRS ≤ 12) Remission Rate (YMRS ≤ 12) Response (50% decrease in YMRS) YMRS Withdrawal 34%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
McIntyre, 2009 ⁹ RCT Multisite 3 continents Industry RoB High 19839993	N = 489 Mean Age 39 Female 43% White 61% BP-I 100% Inpatient (week 1) Outpatient (weeks 2-3, subject to investigator discretion and successful passing of InterSePT Scale for Suicidal Thinking criteria)	Manic/Mixed; YMRS ≥ 20; Current episode ≤ 3 months First Manic Episode Neurological Disorders Substance Abuse Taking Other Meds Labs/Other Conditions	Asenapine 10-20 mg/day (18.2 mg/day) N=104	C1: Placebo n=194 C2: Olanzapine 5-20 mg/day n=190	3 weeks	AIMS BARS CGI-BP-S MADRS Remission (YMRS ≤12) Response (50% decrease in YMRS) Simpson-Angus Scale (SAS) YMRS Withdrawal 31%
Calabrese, 2015 ¹⁰ RCT Multisite 3 Continents Industry RoB Low 25562205	N = 497 Mean Age 42 Female 47% White 69% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3, subject to inspector discretion)	Manic/Mixed; YMRS ≥20 AND ≥ 4 on two YMRS items; MADRS < 18 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds	Cariprazine I1: 3-6 mg/day I2: 6-12 mg/day	Placebo	3 weeks	CGI-S SAS YMRS Withdrawal 11%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Durgam, 2015 ¹¹ RCT Multisite 3 Continents Industry RoB Moderate 25056368	N = 238 Mean Age 38 Female 67% White 43% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3, subject to inspector discretion)	Manic/Mixed; YMRS ≥20 AND ≥4 on two YMRS items First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Cariprazine 3-12 mg/day	Placebo	3 weeks	YMRS MADRS CGI-S CGI-I PANSS AIMS BARS SAS Withdrawal 37%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table E8. Summary risk of bias assessments: asenapine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Asenapine	McIntyre, 2010 ¹² Industry 20096936	High	Randomization and blinding procedures not described. Withdrawal 34%.
	McIntyre, 2009 ⁹ Industry 19839993	High	Randomization and blinding procedures not described. Patients discharged from inpatient care at differing times and study doesn't include this as a point of analysis as a possible confounder. Withdrawal 31%.
	Landbloom, 2016 ⁷ Industry 26496015	Low	No sources of bias identified.

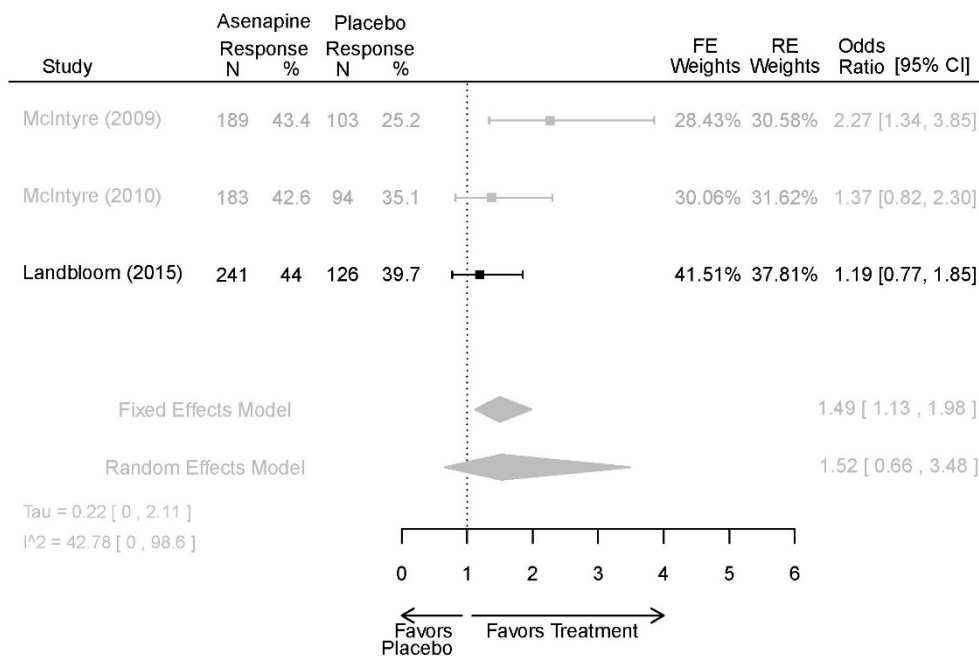
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Asenapine Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

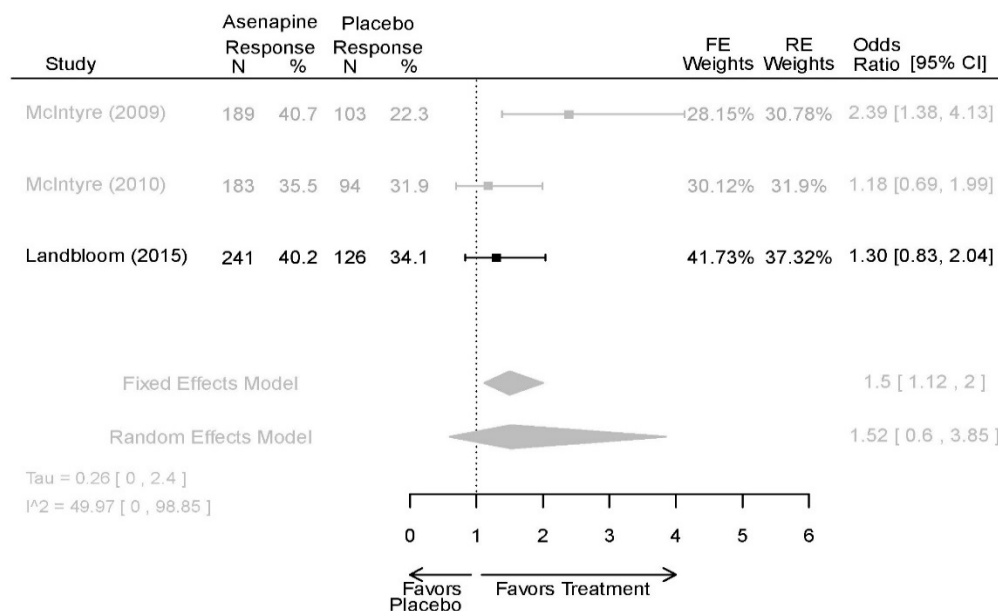
Appendix Figure E20. Asenapine vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



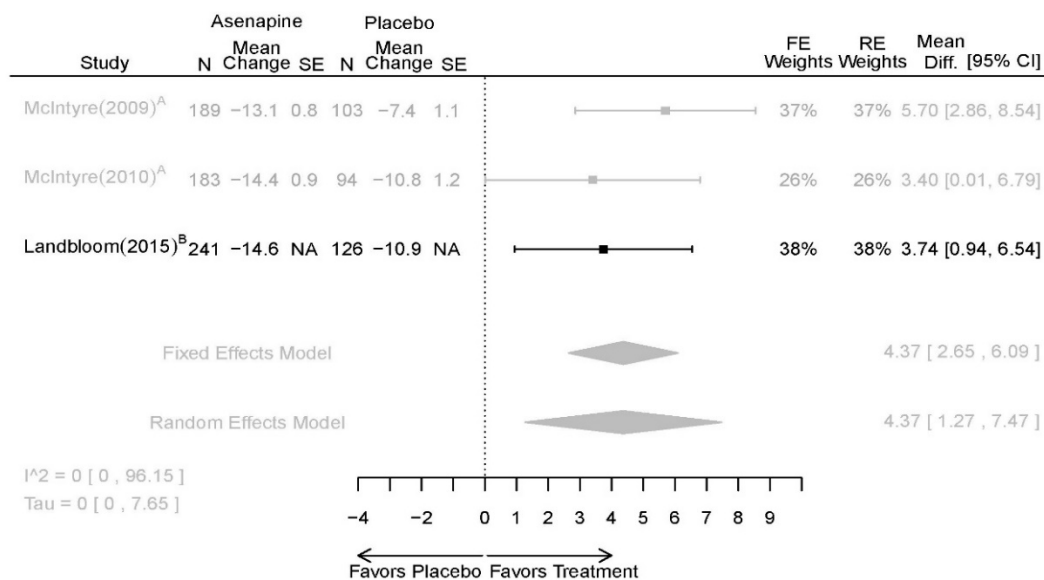
Appendix Figure E21. Asenapine vs. placebo - remission

Odds Ratio of Remission (YMRS ≤ 12) at 3 Weeks



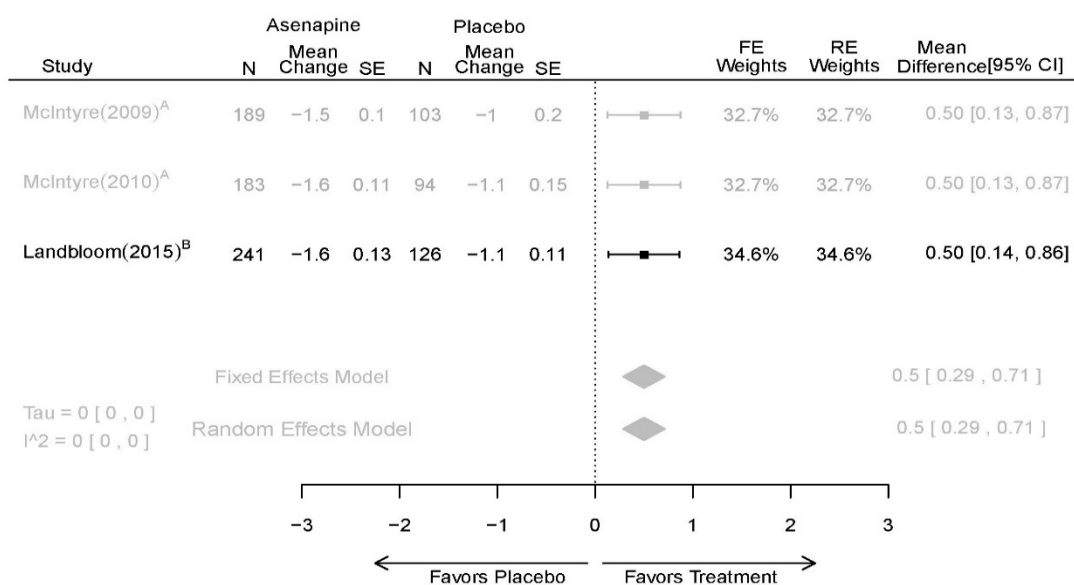
Appendix Figure E22. Asenapine vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to 3 Weeks



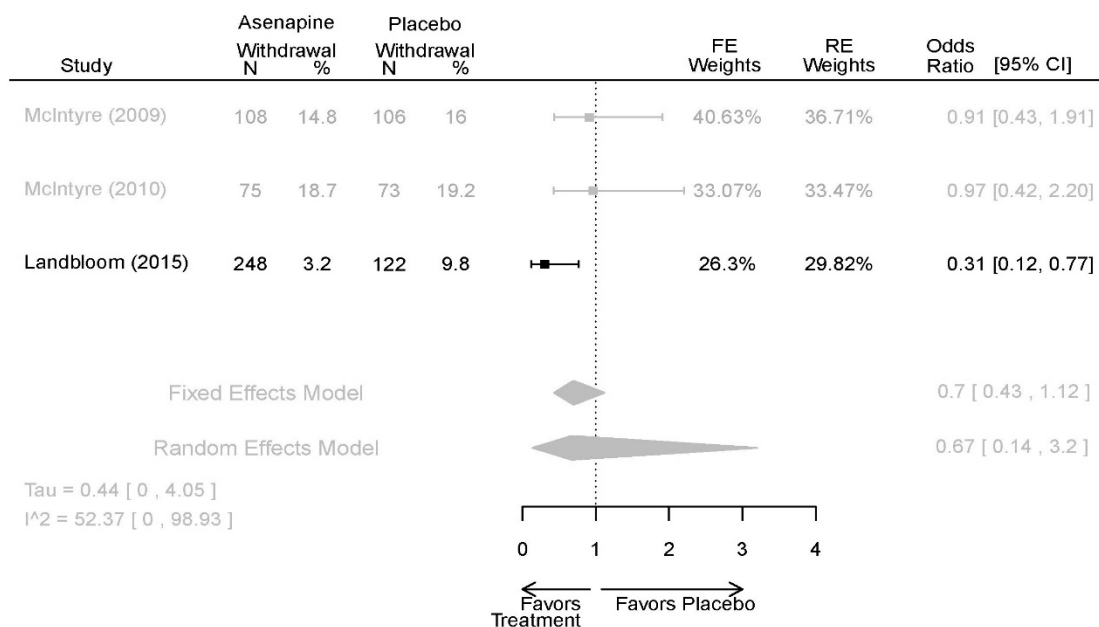
Appendix Figure E23. Asenapine vs. placebo – CGI-BP-S

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks

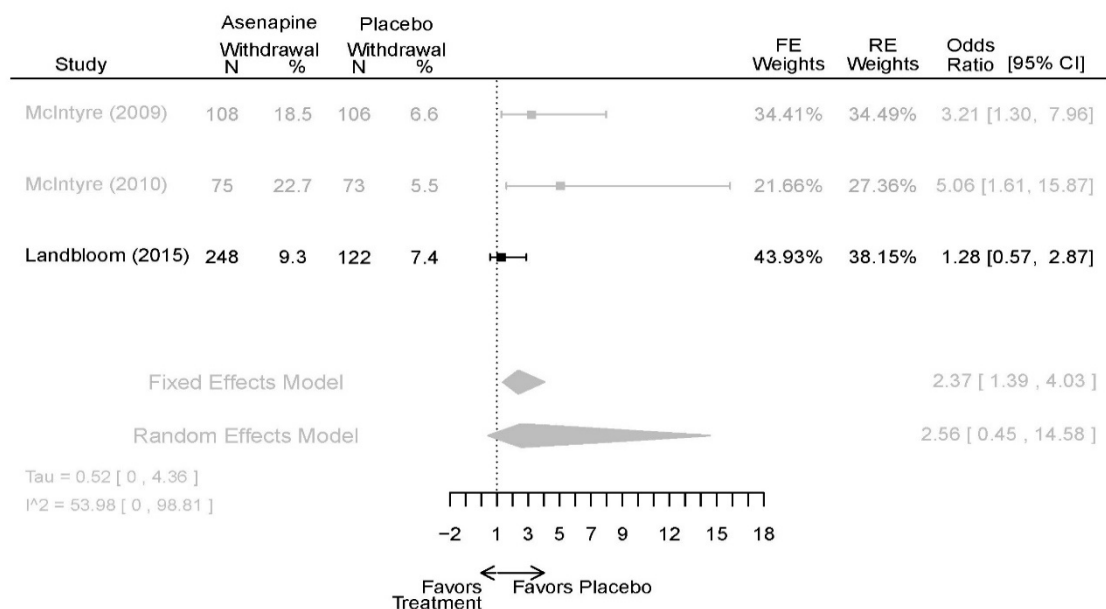


Appendix Figure E24. Asenapine vs. placebo – withdrawal lack of efficacy

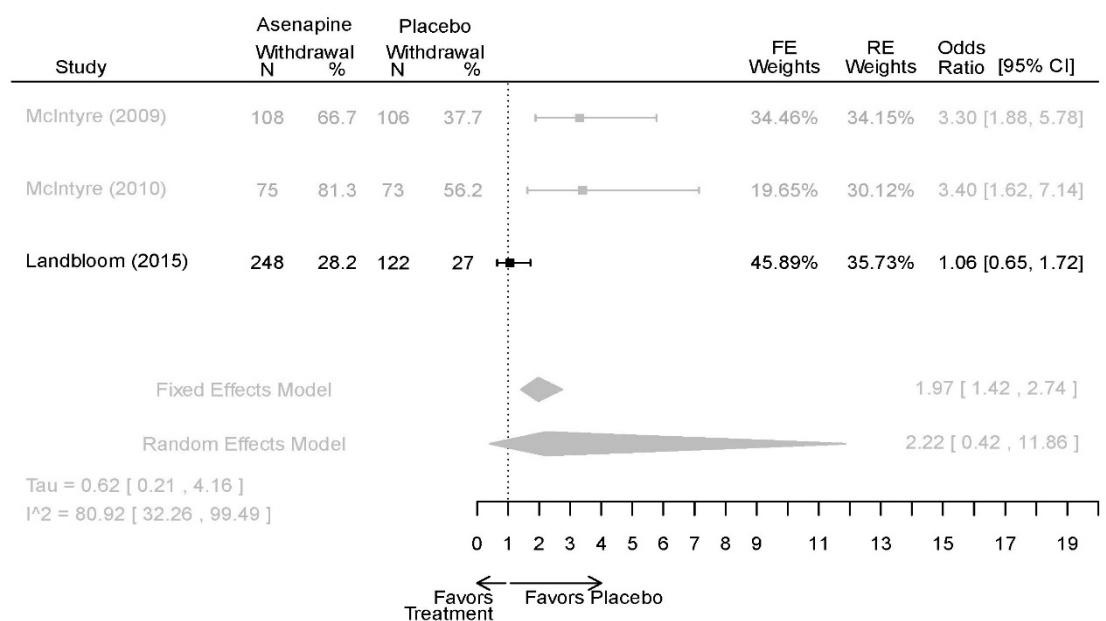
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E25. Asenapine vs. placebo – withdrawal adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E26. Asenapine vs. placebo – overall withdrawal
Odds Ratio of Overall Withdrawal



Appendix Table E9. Outcomes summary: asenapine versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Asenapine	McIntyre, 2010 ¹² Industry 20096936	See forest plot E20 above for response.	See forest plot E22 above for YMRS.	See forest plot E23 above for CGI.	See forest plots E24, E25, E26 above for Withdrawals. 1 suicide in asenapine	SAE Placebo: 3.8% Asenapine: 1.5% NS EPS (≤ 1) Placebo: 3.1% Asenapine: 10.3% p=0.03 Weight gain $\geq 7\%$ Placebo: 1.2% Asenapine: 7.2% p=0.03
	McIntyre, 2009 ⁹ Industry 19839993	See forest plot E20 above for response.	See forest plot E22 above for YMRS.	See forest plot E32 above for CGI.	See forest plots E24, E25, E26 above for Withdrawals.	SAE Placebo: 3.8% Asenapine: 1.5% NS EPS (≤ 1) Placebo: 3.1% Asenapine: 10.3% p=0.03 Weight gain $\geq 7\%$ Placebo: 1.2% Asenapine: 7.2% p=0.03

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Landbloom, 2016 ⁷ Industry 26496015	See forest plot E20 above for response.	See forest plot E22 above for YMRS.	See forest plot E32 above for CGI.	See forest plots E24, E25, E26 above for Withdrawals. Suicide Ideation Placebo: 5/126 5 mg Asenapine: 4/122 10 mg Asenapine: 1/129 NS	SAE "Most...were psychiatric disorders class" Placebo: 2/126 5 mg Asenapine: 3/122 10 mg Asenapine: 1/119 NS EPS Placebo: 6/126 5 mg Asenapine: 8/122 10 mg Asenapine: 25/129 p<0.0001 10 mg

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=c; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E10. Strength of evidence assessment: asenapine versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Asenapine vs. placebo	Response Remission 3 wks	3 RCT (n=936)	NS	Moderate	Consistent	Direct	Imprecise	Low
	YMRS 3 wks	3 RCT (n=936)	Favors Asenapine. MD 4.37 (1.27, 7.47)	Moderate	Consistent	Direct	Imprecise	Low
	CGI-BP-S 3 wk	3 RCT (n=936)	Favors Asenapine MD 0.5 (0.29, 0.71)	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – AE, Lack of Efficacy, Overall	3 RCT (n=936)	NS	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an

assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E11. Outcomes summary: asenapine versus active comparator for acute mania

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Asenapine vs. olanzapine	McIntyre, 2009 ⁹ 19839993	<u>Response</u> 3 weeks Asenapine 42.3% Olanzapine 50% <u>Remission</u> 3 weeks Asenapine 40.2% Olanzapine 39.4% NS	<u>YMRS</u> 3 weeks Least square mean Asenapine -10.8 SD 0.8 (effect size 0.45) Olanzapine -12.6 SD 0.8 (effect size 0.70)	<u>CGI</u> 3 weeks Least square mean Asenapine -1.2 SD 0.01 Olanzapine -1.4 SD 0.01	NR <u>Overall Withdrawal</u> Asenapine 37.1% Olanzapine 30.9% Withdrawal Lack of Efficacy: Asenapine 8.2% Olanzapine 5.8% Withdrawal AE Asenapine 10.3% Olanzapine 4.2%	<u>Serious Adverse Events</u> 3 weeks 0 in all arms <u>Deaths</u> 3 weeks 0 in all arms <u>EPS</u> 3 weeks 2.9% placebo 7.2% Asenapine 7.9% Olanzapine
	McIntyre, 2010 ¹² 20096936	<u>Response</u> 3 weeks Asenapine 42.6% Olanzapine 54.7% <u>Remission</u> 3 weeks Asenapine 35.5% Olanzapine 46.3% NS	<u>YMRS</u> 3 weeks Least square mean Asenapine -11.5 SD 0.8 (effect size 0.32) Olanzapine -14.6 SD 0.8 (effect size 0.63)	<u>CGI</u> 3 weeks Least square mean Asenapine -1.2 SD 0.10 Olanzapine -1.5 SD 0.09	NR <u>Overall Withdrawal</u> Asenapine 33.0% Olanzapine 21.5% Withdrawal Lack of Efficacy: Asenapine 7.6% Olanzapine 6.3% Withdrawal AE Asenapine 9.2% Olanzapine 3.4%	<u>Serious Adverse Events</u> 3 weeks 1 Asenapine <u>Deaths</u> 3 weeks 1 Asenapine – suicide <u>EPS</u> 3 weeks 3.1% placebo 10.3% Asenapine 6.8% Olanzapine

Abbreviations: CGI=Clinical Global Impressions; EPS=extrapyramidal symptoms; NR=not reported; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Appendix Table E12. Strength of evidence assessment: asenapine versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Asenapine vs. olanzapine	Response 3 wk Remission 3 wk YMRS 3 wk CGI Withdrawal	2 RCTs (n=763)	See table above	High	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 3. Cariprazine for Acute Mania

Appendix Table E13. Characteristics of eligible studies: cariprazine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Calabrese, 2015 ¹⁰ RCT Multisite 3 Continents Industry RoB Low 25562205	N = 497 Mean Age 42 Female 47% White 69% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3, subject to inspector discretion)	Manic/Mixed; YMRS ≥ 20 AND ≥ 4 on two YMRS items; MADRS < 18 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds	Cariprazine I1: 3-6 mg/day I2: 6-12 mg/day	Placebo	3 weeks	CGI-S SAS YMRS Withdrawal 11%
Durgam, 2015 ¹¹ RCT Multisite 3 Continents Industry RoB Moderate 25056368	N = 238 Mean Age 38 Female 67% White 43% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3, subject to inspector discretion)	Manic/Mixed; YMRS ≥ 20 AND ≥ 4 on two YMRS items First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Cariprazine 3-12 mg/day	Placebo	3 weeks	YMRS MADRS CGI-S CGI-I PANSS AIMS BARS SAS Withdrawal 37%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Sachs, 2015 RCT Multisite 2 Continents Industry RoB Moderate 25532076	N = 312 Mean Age 36 Female 36% White 21% BP-I 100% Inpatient (weeks 1-2) Outpatient (week 3, subject to inspector discretion)	Manic/Mixed; YMRS ≥20 AND ≥4 on two YMRS items; MADRS <18 Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing	Cariprazine 3-12 mg/day	Placebo	3 weeks	YMRS CGI-S CGI-I MADRS PANSS C-SSRS AIMS BARS SAS Withdrawal 31%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table E14. Summary risk of bias assessments: cariprazine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Cariprazine	Durgam, 2015 ¹¹ Industry 25056368	Moderate	The large dropout rate is likely to create some bias. Lack of disclosure of methods to allocate and protect the blind also increases the risk.
	Calabrese, 2015 ¹⁰ Industry 25562205	Low	Procedures for concealing allocation and blinding participants and providers are not described, but, the study appears to have been well executed, fully reported, and investigators have taken steps to ensure bias was minimized, like pattern mixture modeling.
	Sachs, 2015 ¹³ Industry 25532076	Moderate	A moderately high dropout rate combined with a lack of disclosure for the methods of allocation and concealment create strong conditions where bias may be present.

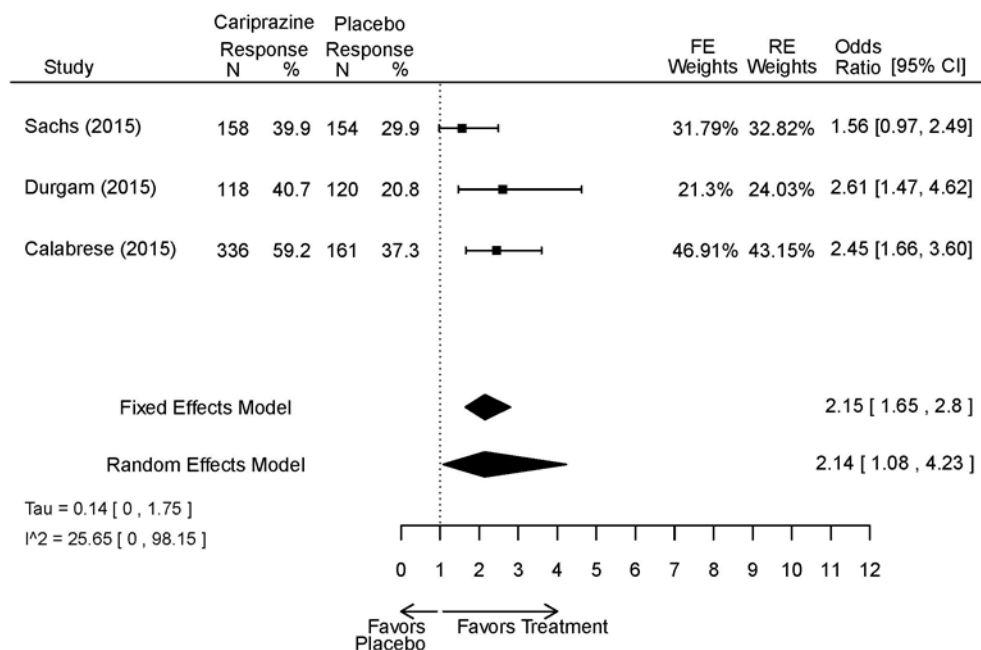
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Cariprazine Forest Plots

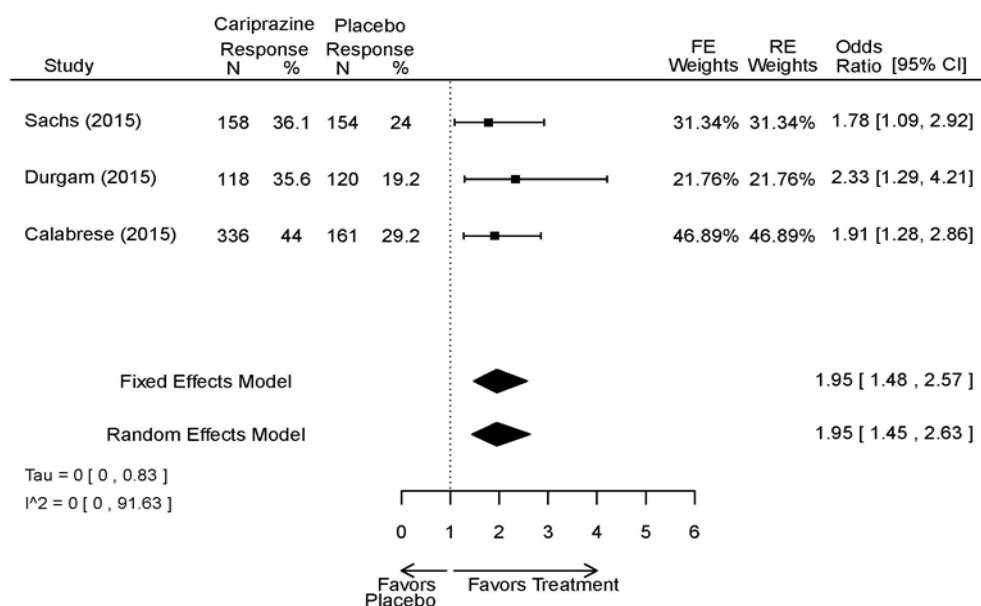
Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

Appendix Figure E27. Cariprazine vs. placebo – response

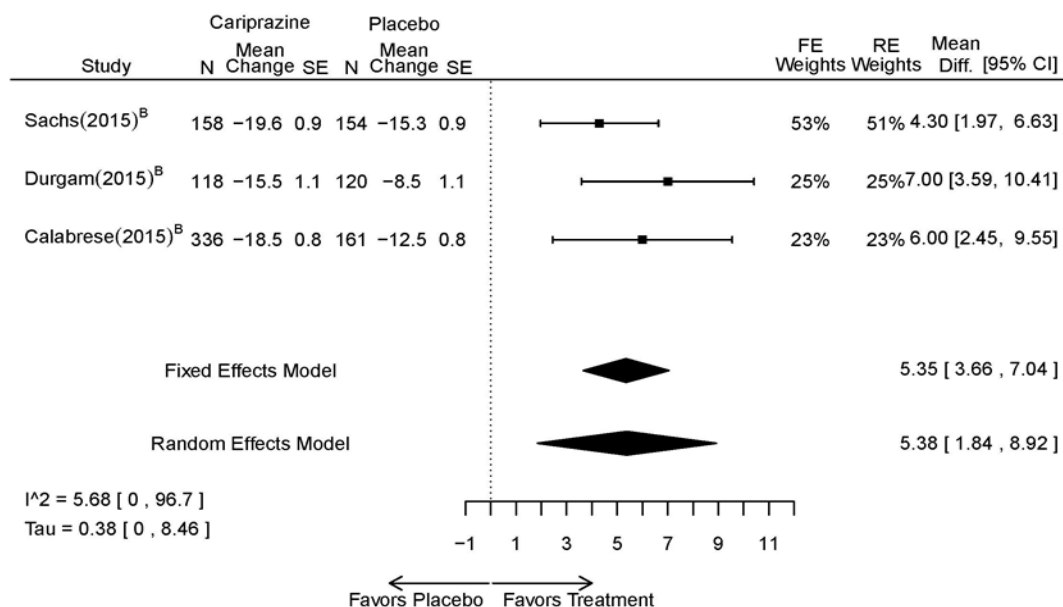
Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



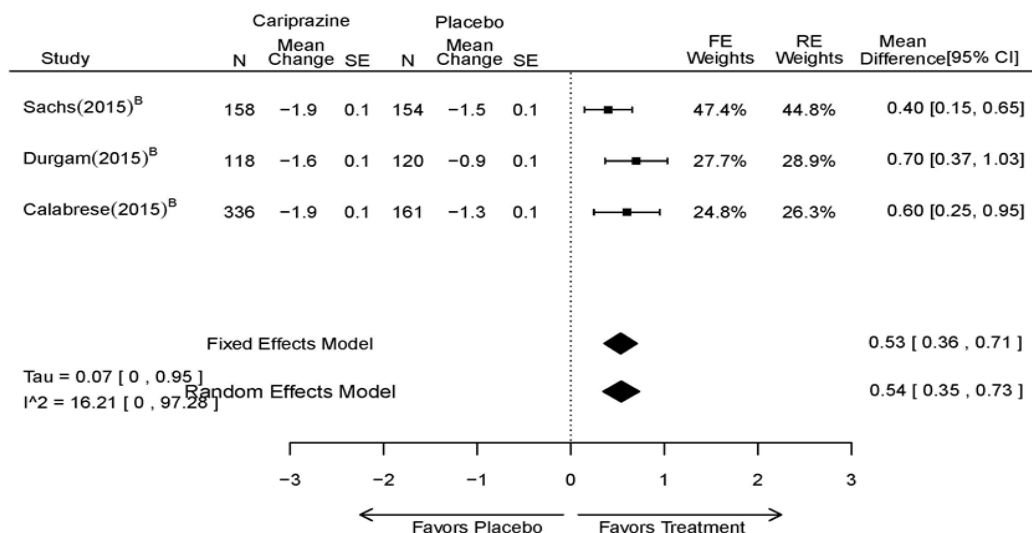
Appendix Figure E28. Cariprazine vs. placebo - remission
Odds Ratio of Remission (YMRS ≤ 12) at 3 Weeks



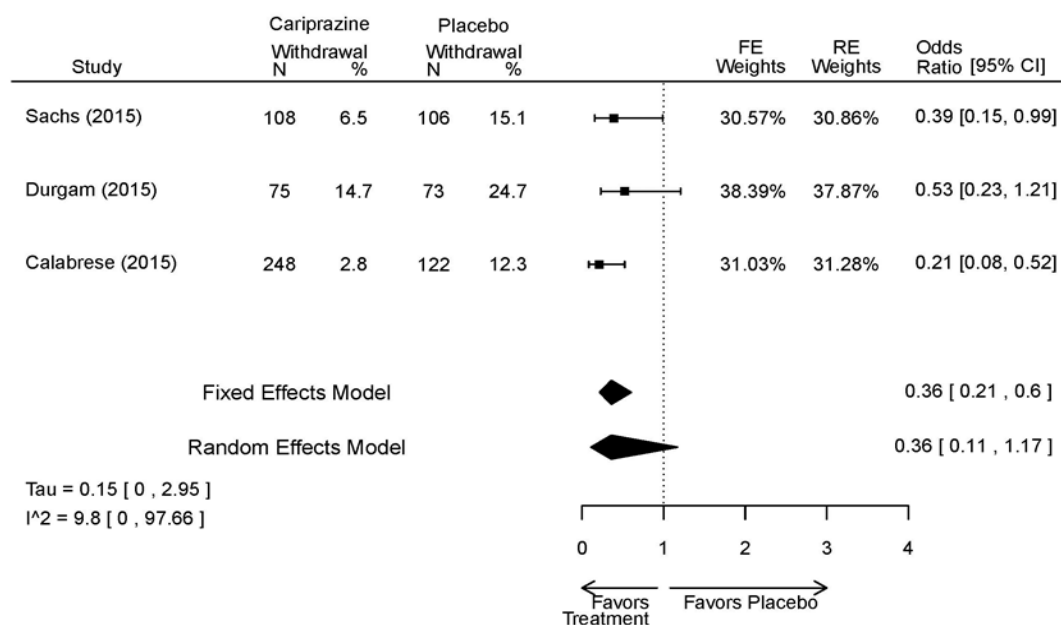
Appendix Figure E29. Cariprazine vs. placebo – YMRS
Difference in Mean Change in YMRS from Baseline to 3 Weeks



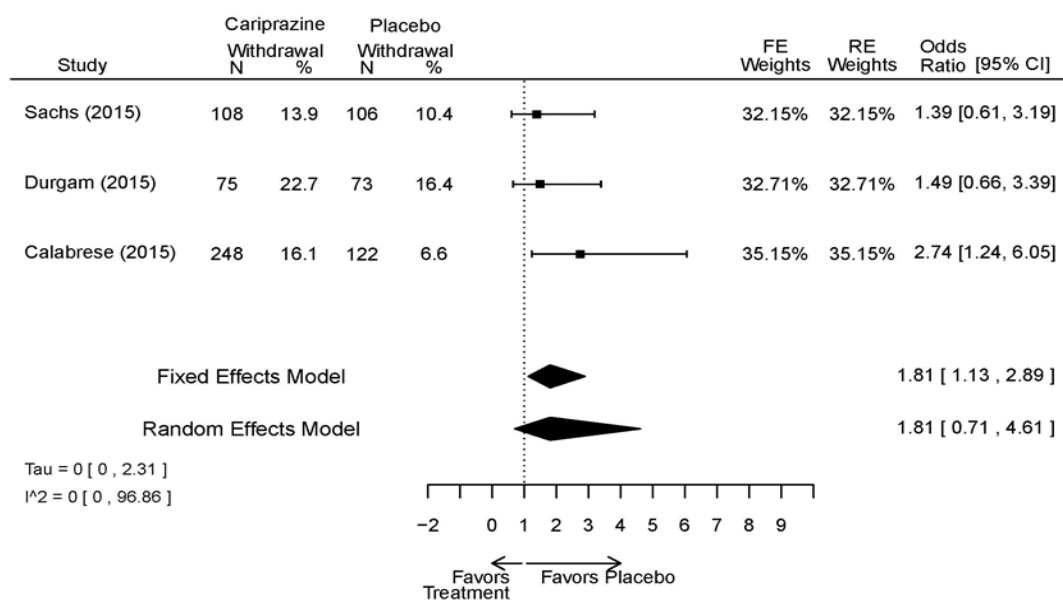
Appendix Figure E30. Cariprazine vs. placebo – CGI-BP-S
Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks



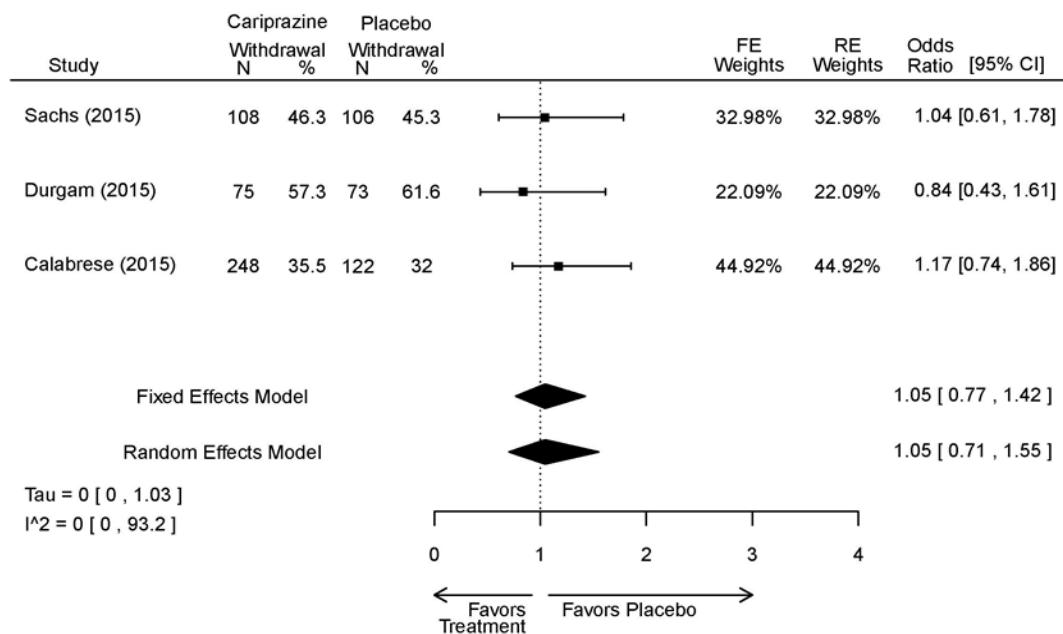
Appendix Figure E31. Cariprazine vs. placebo – withdrawal lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E32. Cariprazine vs. placebo – withdrawal adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E33. Cariprazine vs. placebo – overall withdrawal
Odds Ratio of Overall Withdrawal



Appendix Table E15. Outcomes summary: cariprazine versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Cariprazine	Durgam, 2015 ¹¹ Industry 25056368	See forest plot E27 above for response.	See forest plot E29 above for YMRS.	See forest plot E30 above for CGI.	See forest plots E31, E32, E33 above for Withdrawals.	SAE Placebo: 5 patients Cariprazine: 4 patients No suicide attempts No difference between groups in suicide ideation EPS Placebo: 1% Cariprazine groups: 11% or 14% Akathesia Placebo: 4% Cariprazine groups:20% or 23%
	Calabrese, 2015 ¹⁰ Industry 25562205	See forest plot E27 above for response.	See forest plot E29 above for YMRS.	See forest plot E30 above for CGI.	See forest plots E31, E32, E33 above for Withdrawals.	SAE Placebo: 0 patients Cariprazine: 4 patients No suicide attempts 1 placebo patients reported suicide ideation EPS Placebo: 1 patient Cariprazine: 19 patients Akathesia Placebo: 7 patient Cariprazine: 26 patients

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Sachs, 2015 ¹³ Industry 25532076	See forest plot E27 above for response.	See forest plot E29 above for YMRS.	See forest plot E30 above for CGI.	See forest plots E31, E32, E33 above for Withdrawals.	SAE Placebo: 3 patients Cariprazine: 5 patients No suicide attempts No difference between groups in suicide ideation EPS Placebo: 6 patients Cariprazine: 30 patients Akathisia Placebo: 8 patient Cariprazine: 36 patients

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E16. Strength of evidence assessment: cariprazine versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cariprazine vs. placebo	Response 3 wks	3 RCT (n=1,047)	Favors Cariprazine OR 2.14 (95% CI 1.08, 4.23)	Moderate	Consistent	Direct	Imprecise	Low
	Remission 3 wks	3 RCT (n=1,047)	Favors Cariprazine OR 1.95 (95% CI 1.45, 2.63)	Moderate	Consistent	Direct	Imprecise	Low
	YMRS 3 wks	3 RCT (n=1,047)	Favors Cariprazine MD 5.38 (95% CI 1.84, 8.92)	Moderate	Consistent	Direct	Imprecise	Low

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
	CGI-BP-S 3 wk	3 RCT (n=1,047)	Favors Cariprazine MD 0.54 (95% CI 0.35, 0.73)	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – AE, Lack of Efficacy, Overall	3 RCT (n=1,047)	NS	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 4. Haloperidol for Acute Mania

Appendix Table E17. Characteristics of eligible studies: haloperidol for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
McIntyre, 2005 ¹⁴ RCT Multisite 3 Continents Industry Moderate 16139175	N = 299 Mean Age 42 Female 63% Race NR BP-I 100% Inpatient	Manic YMRS \geq 20 CGI-BP \geq 4 First Manic Episode Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Haloperidol Starting 2mg/day up to 8mg/day	C1: Placebo C2: Quetiapine 100mg/day increasing by 100mg up to 800 mg/day	12 weeks	Remission Rates Adverse Events Efficacy YMRS CGI PANSS MADRS GAS Withdrawal 50%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Smulevich, 2005 ¹⁵ RCT Multisite Location NR Industry Moderate 15572276	N = 438 Mean Age 40 Female 47% White 65% BP-I 100% Outpatient	Manic YMRS \geq 20 MADRS \leq 20 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Taking Other Meds	Haloperidol Initiated at 4mg/day increased by 2mg/day up to 12 mg/day	C1: Placebo C2: Risperidone Initiated at 2mg/day increased by 1mg/day up to 6mg/day	12 weeks (12 week outcomes excluded due to attrition of Haloperidol arm)	Efficacy YMRS CGI GAS MADRS BPRS Extrapyramidal symptoms ESRS Withdrawal 48% at 12 weeks 12% at 3 weeks

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trials; YMRS = Young Mania Rating Scale

Appendix Table E18. Summary risk of bias assessments: haloperidol for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Haloperidol	McIntyre, 2005 ¹⁶ Industry 16139175	High	High dropout rates (46% overall) create a likelihood of bias, lacks some core information on how allocation was concealed and blinding of treatment staff and raters was maintained.
	Smulevich, 2005 ¹⁵ Industry 15572276	Moderate	Open drugs given to some participants. Pools results for blinded and unblinded without establishing similarity of groups
	Sachs, 2002 ¹⁷ Industry 12091192	High	Lacks randomization and blinding procedures. High dropout rates across all arms (46% overall)
	Vieta, 2010 ¹⁸ Industry 20565430	High	Large dropout rate among all study arms, across all time periods; raters may not be blinded

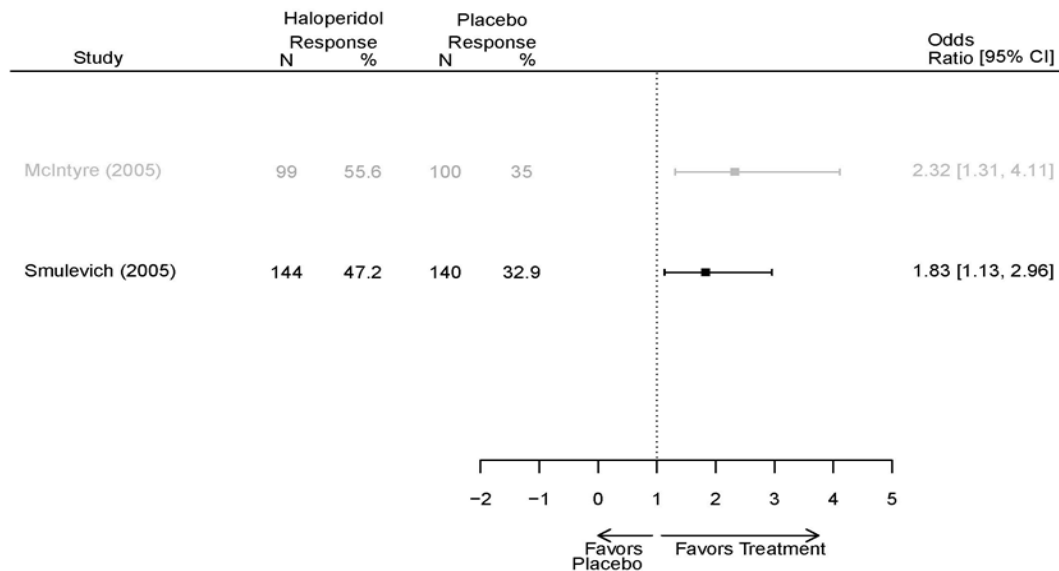
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Haloperidol Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

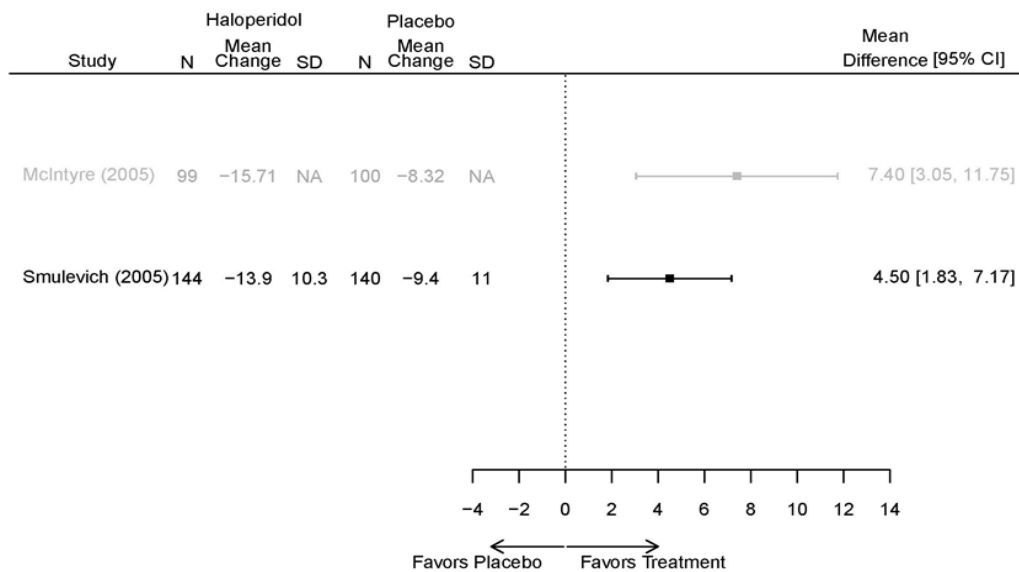
Appendix Figure E34. Haloperidol vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



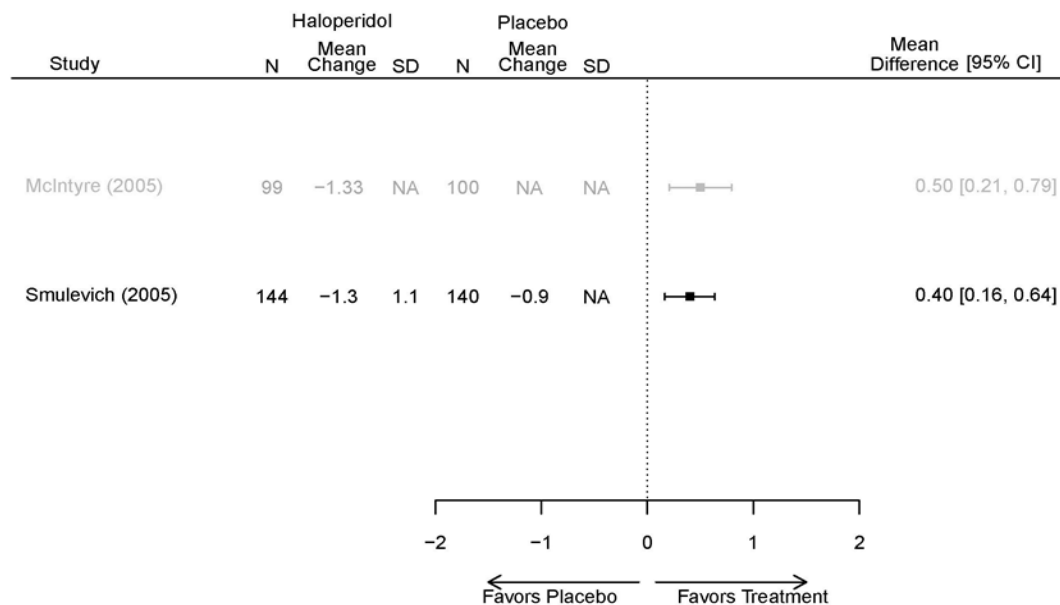
Appendix Figure E35. Haloperidol vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to Last Measurement

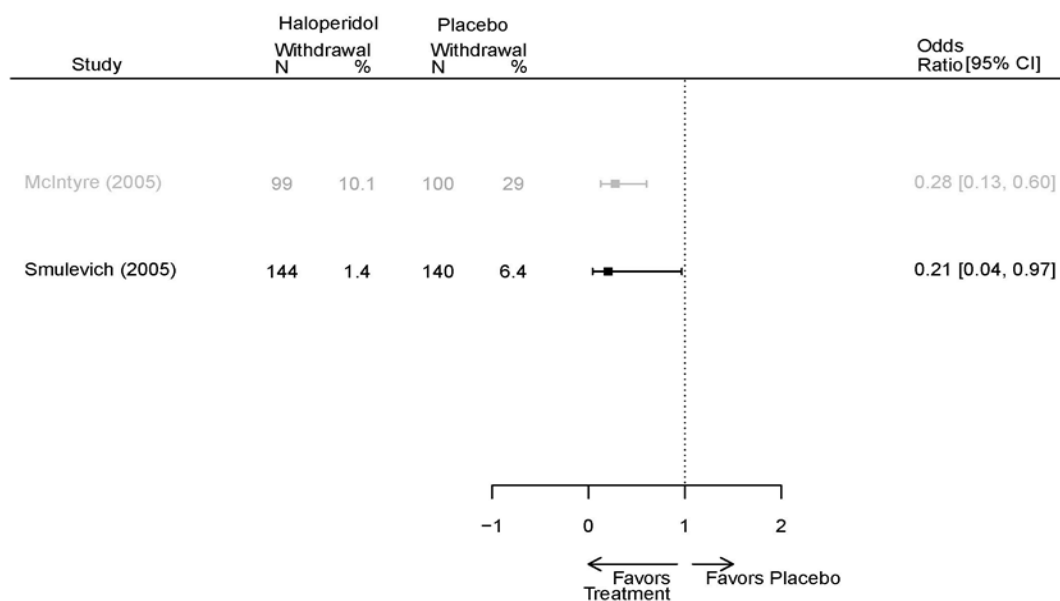


Appendix Figure E36. Haloperidol vs. placebo – CGI-BP-S

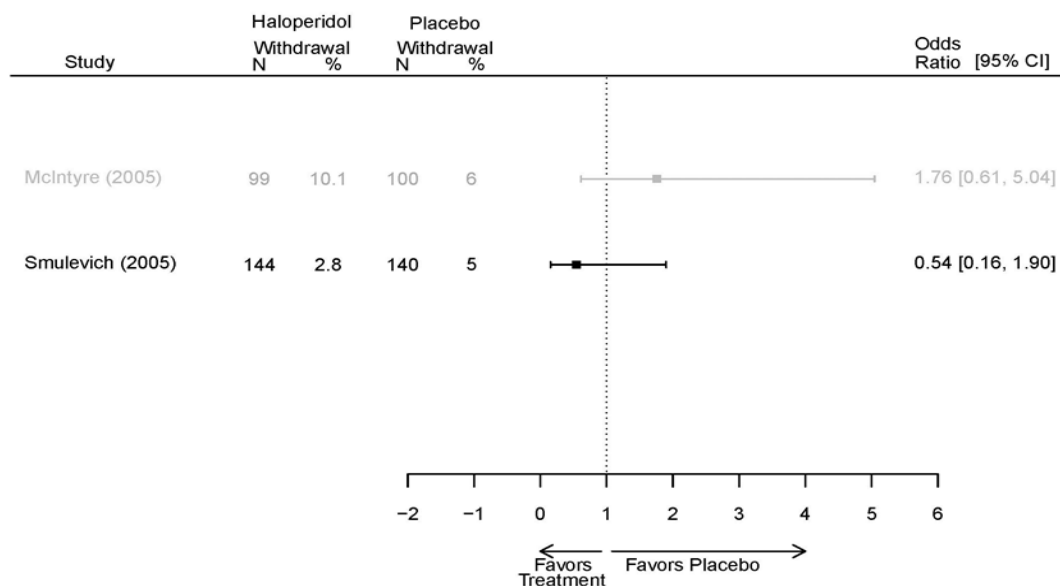
Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to Last Measurement



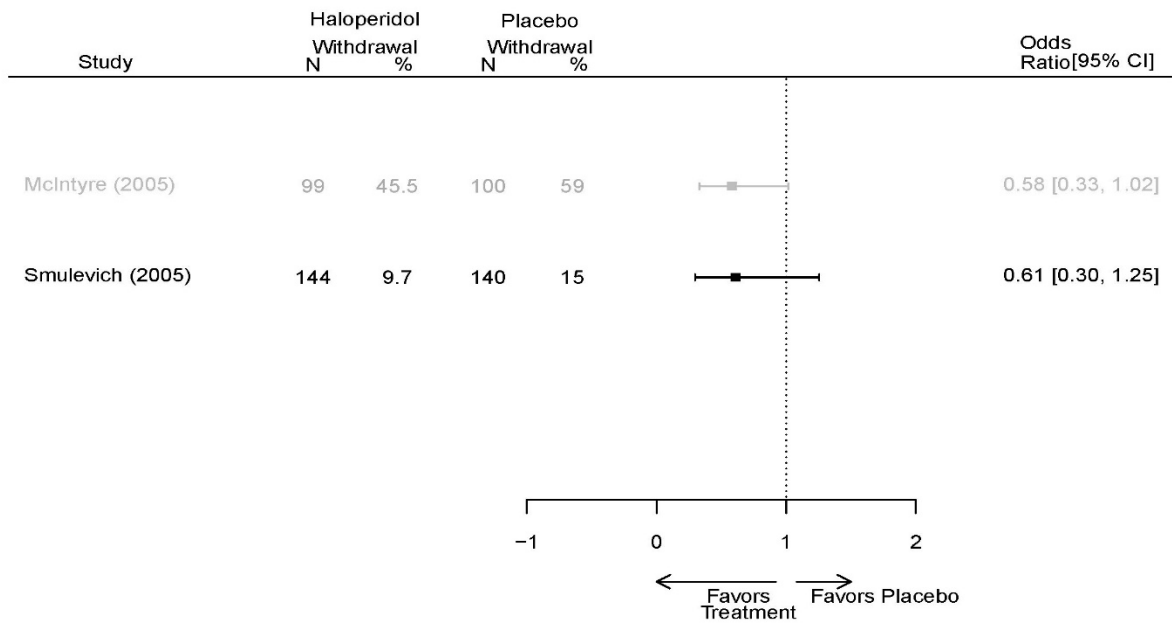
Appendix Figure E37. Haloperidol vs. placebo – withdrawal lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E38. Haloperidol vs. placebo – withdrawal adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E39. Haloperidol vs. placebo – overall withdrawal
Odds Ratio of Overall Withdrawal



Appendix Table E19. Outcomes summary table: haloperidol versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Haloperidol	McIntyre, 2005 ¹⁴ 16139175 High	<u>Response</u> See forest plot E34 above for response <u>Remission</u> NS	See forest plot E35 above for YMRS	See forest plot E36 for CGI	See forest plot E37, E38, E39 above for Withdrawals	<u>SAE</u> No reported serious events EPS Haloperidol 35.4% Placebo 5.9% P<0.001 Weight gain 7% NS
	Smulevich, 2005 ¹⁵ 15572276 Moderate	<u>Response</u> See forest plot E34 above for response <u>Remission</u>	See forest plot E35 above for YMRS	See forest plot E36 for CGI <u>GAS</u> 3 week Placebo -10.3(1.7) Haloperidol - 13.9(10.3) No Statistical Tests reported <u>GAS</u> 12 week Placebo Haloperidol No Statistical Tests reported	See forest plot E37, E38, E39 above for Withdrawals	<u>No reported SAE</u>

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E20. Strength of evidence assessment: Haloperidol versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Haloperidol vs. placebo	Relapse 3 wks YMRS CGI-BP-S Withdrawals	2 RCTs (n=483)	See forest plots	High	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 5. Olanzapine for Acute Mania

Appendix Table E21. Characteristics of eligible studies: olanzapine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Xu, 2015 ¹⁹ RCT Single-site Government RoB Low 26060401	N = 120 Mean Age 31 Female 52% Race NR BP-I 100% Setting NR	First manic; YMRS ≥ 17 Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing	Olanzapine 10 mg/day Flexible dosing 5-20 mg/day	C1: Olanzapine 10 mg/day + Valproate 600 mg/day C2: Valproate 600 mg/day alone	4 weeks	Efficacy YMRS CGI-BP Adverse events Extrapyramidal symptoms SAS Withdrawal 5%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Katagiri, 2012 ²⁰ RCT Single Site Japan Industry RoB Moderate 22134043	N = 221 Mean Age 45 Female 55% Race NR BP-I 100% Outpatient	Manic or Mixed Episode YMRS ≥ 20 Other Mental Health Taking Other Meds Labs/Other Conditions	Olanzapine Initiated at 10mg/day (5-20mg/day)	Placebo (Haloperidol arm not used <10 per arm completed)	3 weeks (6 week not abstracted due to attrition)	Adverse Events Extrapyramidal symptoms DIEPSS Efficacy YMRS HAM-D CGI Withdrawal 41% at 3 weeks 52% at 6 weeks
Vieta, 2012 ²¹ RCT Multisite 4 Continents Industry RoB High 22503488	N = 560 Mean Age 37 Female 52% White 41% BP-I 100% Outpatient	Manic or Mixed Episode; Acute (YMRS ≥ 20 and CGI-S ≥ 4) or non-acute (mood episodes with YMRS <12 and CGI-S ≤3)	Olanzapine 10 mg/day	C1: Placebo C2: Risperidone long- acting injectable (25- 50 mg)	12 weeks (18 month extension for participants without mood recurrence)	Response (YMRS ≤ 19) Time to first recurrence of mood symptoms Efficacy YMRS CGI-S MADRS Adverse events Extrapyramidal symptoms ESRS Withdrawal 29%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
McIntyre, 2010 ⁸ RCT Multisite 3 Continents Industry RoB High 20096936	N = 488 Mean Age 39 Female 47% White 55% BP-I 100% Inpatient and Outpatient	Manic or Mixed Episode; YMRS ≥ 20 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Olanzapine 5-20 mg/day	C1: Placebo C2: Asenapine 5-10 mg/2 times daily	3 weeks	Response (≥ 50% YMRS reduction) Time to response (days from baseline to ≥50% YMRS reduction) Remission (≤ 12 YMRS) Efficacy YMRS CGI (BP and mania subscales) MADRS Adverse events Extrapyramidal symptoms SAS BAS AIMS Withdrawal 34%
Shafti, 2010 RCT Iran Funding NR RoB Moderate 19740546	N = 40 Age NR Female 100%; Race NR BP-I 100% Inpatient	Manic (not described) Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Labs/Other Conditions	Olanzapine 5 mg/day	Lithium 300 mg/day	12 weeks	MSRS CGI-S Adverse events Extrapyramidal symptoms Withdrawal 13%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
McIntyre, 2009 RCT Multisite 3 Continents Industry RoB High 19839993	N = 489 Mean Age 40 Female 43% White 61% BP-I 100% Inpatient and Outpatient	Manic or Mixed Episode; YMRS ≥ 20 Schizoaffective Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Olanzapine 5-20 mg/day	C1: Placebo C2: Asenapine 5-10 mg/2 times daily	3 weeks	Response (YMRS, cutoff NR) Remission (YMRS, cutoff NR) Efficacy YMRS CGI (multiple subscales) MADRS Adverse events Extrapyramidal symptoms SAS BAS AIMS Withdrawal 31%
Niufan, 2008 ²² RCT Multisite China Industry RoB Low 17531327	N = 140 Mean Age 33 Female 74% Race NR Diagnosis NR Outpatient	Manic or Mixed Episode; YMRS ≥ 20 NR	Olanzapine 15 mg/day Flexible dosing 5–20 mg/day	Lithium Carbonate 300-600 mg/day Flexible dosing 600-1800 mg/day divided dose	4 weeks	Efficacy YMRS CGI BPRS MADRS Extrapyramidal symptoms SAS Withdrawal 15%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2008 ^{b23} RCT 3 Continents Industry RoB Low 19014751	N = 521 Mean Age 40 Female 49% Race NR Diagnosis NR Inpatient and Outpatient	Manic or Mixed Episode; YMRS 20-30 CGI-BP mania 3-4 Schizoaffective Other Mental Health Pregnant/Nursing	Olanzapine 5-20 mg/day	C1: Placebo C2: Divalproex 500- 2500 mg/2-3 times daily	12 weeks	Response (≥ 50% YMRS reduction) Time to response (days from baseline to ≥ 50% YMRS reduction) Remission (≤ 12 YMRS) Efficacy YMRS CGI (multiple subscales) MADRS Adverse events Extrapyramidal symptoms SAS BAS AIMS Withdrawal 26%
Perlis, 2006 ²⁴ RCT Multisite US Industry RoB High 17196055	N = 329 Mean Age 38 Female 55% White 74% BP-I 100% Outpatient	Manic; YMRS ≥ 20 Substance Abuse Labs/Other Conditions	Olanzapine 5–20 mg/day	Risperidone 1–6 mg/day	3 weeks	Efficacy YMRS MADRS CGI HAM-D DAI-10 PGWB SF-12 Extrapyramidal symptoms BAS Simpson-Angus Withdrawal 27%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Revicki, 2003 ²⁵ RCT Multisite US Industry RoB Moderate 12716270 Secondary analysis of Zajecka 2002 [PMID 12523875]	N = 52 Mean Age 38 Female 56% White 81% BP-I 100% Inpatient and outpatient	Manic; YMRS ≥ 25	Olanzapine 20 mg/day	Divalproex 20 mg/kg/day up to an additional 1000 mg/day	12 weeks (6 and 12 week outcomes excluded due to attrition)	Efficacy YMRS Quality of Life HRQL Q-LES-Q Medical Resource Use Cost Withdrawal (base study Zajecka, 2002 reports withdrawal of 69% at 12 weeks, Revicki reports 35% withdrawal at 3 weeks)
Tohen, 2003 ²⁶ RCT Multisite 4 Continents Industry RoB Moderate 14662554 12177585 ²⁷	N = 453 Mean Age 40 Female 60% Race NR BP-I 100% Inpatient or outpatient	Manic; YMRS ≥ 20 Substance Abuse Labs/Other Conditions	Olanzapine 15 mg/day flex dosing 5, 10,15, or 20 mg/day	Haloperidol 10 mg/day flex dosing 3, 5, 10, or 15 mg/day	12 weeks	Illness Severity YMRS HAM-D Quality of Life SF-36 Extrapyramidal Symptoms AIMS BAS Remission Adverse Events Withdrawal 43%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2002b ²⁸ RCT Multisite US Industry RoB High 12042191	N = 251 Mean Age 41 Female 57% White 81% BP-I 100% Outpatient	Mania; YMRS ≥ 20 Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Olanzapine 15 mg/day with flexible dosing from 5-20 mg/day	Divalproex 750mg/day with flexible dosing from 500–2500 mg/day	3 weeks	Efficacy YMRS HAM-D Remission Adverse Events Extrapyramidal symptom Withdrawal 34%
Tohen, 2000 ²⁹ RTC Multisite US Industry RoB High 10986547	N = 115 Mean Age 39 Female 50% White 80% Diagnosis NR Inpatient (week 1) Outpatient (after week 1 if CGI-BP ≤3)	Mixed Episode; YMRS score ≥ 20 Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Meds; Labs/Other Conditions	Olanzapine 15 mg/day (adjusted between 5-20 mg/day)	Placebo	4 weeks	Symptom Severity YMRS HAM-D CGI PANSS Safety EPS Adverse Events Withdrawal 49%
Berk, 1999 ³⁰ RCT Single-Site South Africa University RoB High 10565800	N = 30 Mean Age 31 Sex NR Race NR Diagnosis NR Inpatient	Mania (no other inclusion criteria provided) Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	Olanzapine 10 mg/day	Lithium 400mg twice /day	4 weeks	Psychiatric Condition PRS CGI MAS Functioning GAF Side Effects SAS Withdrawal NR

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale;

DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table E22. Summary risk of bias assessments: olanzapine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Olanzapine	Xu, 2015 ¹⁹ Government 26060401	Low	Well-constructed, described, and reported study. 5% dropout.
	Katagiri, 2012 ³¹ Industry 22134043	Moderate	Appears to be completely reported and generally well executed, however, dropout rates and LOCF create substantial possibility for bias.
	Vieta, 2012 ³² Industry 22503488	High	High - blinding and randomization procedures not well described. Period II results are biased by the drug assignment being open label. Period three efficacy scores are likely to be biased by the large non-completer rate.
	McIntyre, 2010 ¹² Industry 20096936	High	Randomization and blinding procedures not described. 34% dropout.
	Shafiti, 2010 ³³ Funding NR 19740546	Moderate	Randomization and blinding procedures not described. 13% dropout
	McIntyre, 2009 ⁹ Industry 19839993	High	Randomization and blinding procedures not described. Patients discharged from hospital at differing times and doesn't account for this as a possible confounder. 31% overall dropout with high differential dropout between olanzapine and other groups.
	Niufan, 2008 ²² Industry 17531327	Low	Randomization procedure not described. Medication and rater blinded. 16% dropout.
	Tohen, 2008b ²³ Industry 19014751	Low	Well-constructed and described study. No obvious sources of bias present. 26% dropout.
	Perlis, 2006 ³⁴ Industry 17196055	High	Randomization and blinding procedure not described. 27% dropout.

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
	Revicki, 2003 ²⁵ Industry 12716270	Moderate	Randomization and blinding procedures not described. 35% before 3 weeks, 52/120 complete 12 week study. Study notes consistency in traits between dropouts and those who complete, which may be an indication that outcomes may be less biased.
	Tohen, 2003 ²⁶ Industry 14662554	Moderate	Randomization procedure not described. 43% dropout.
	Shi, 2002 ²⁷ Industry 12177585	High	Randomization procedure not described, although does note "randomization codes". States that 166 olanz and 141 halo complete 6 weeks and 140 olanz and 116 halo complete 12 weeks. The counts of patients who complete the follow-up assessments do not match these numbers, in some cases quite substantially. Missing patients not accounted for. Described in the methods that only patients who completed the questionnaire and provided data about the change from baseline to endpoint were included -- not ITT.
	Tohen, 2002b ²⁸ Industry 12042191	High	Randomization and blinding procedures not described. 33% dropout.
	Tohen, 2000 ²⁹ Industry 10986547	High	Blinding procedures not described. Responders allowed to leave hospital, non-responders were not. 49% Dropout.
	Berk, 1999 ³⁰ University 10565800	High	Randomization and blinding procedures not described. Does not describe handling of participants who drop out. Notes that the groups were matched at baseline by education, marital status, ethnicity, employment status but offers no details on these demographic rates.

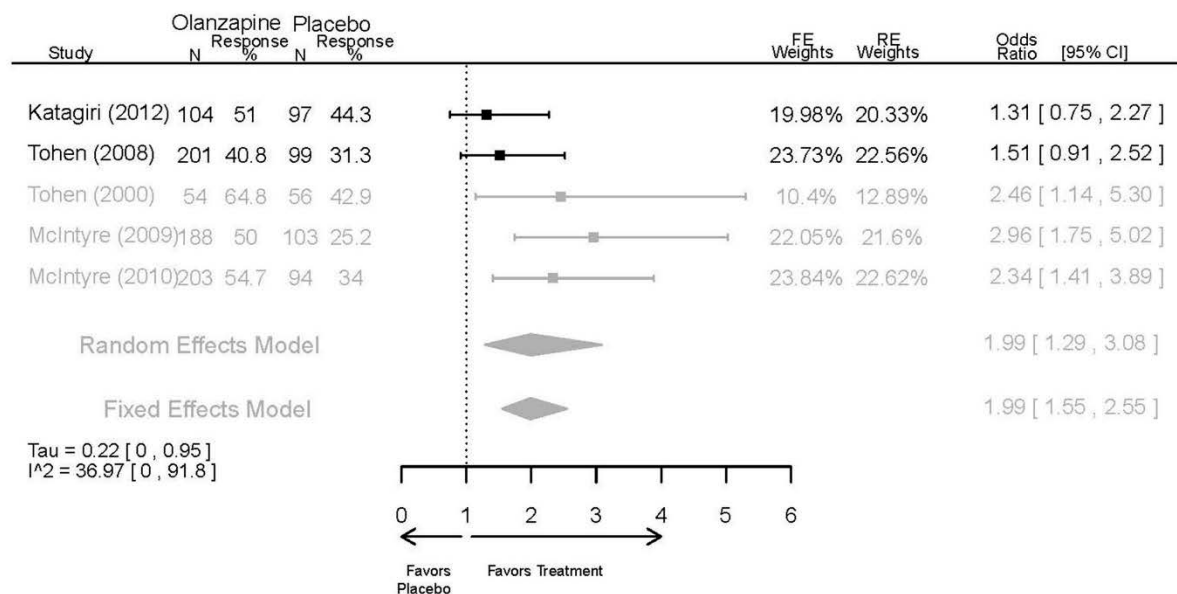
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Olanzapine Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

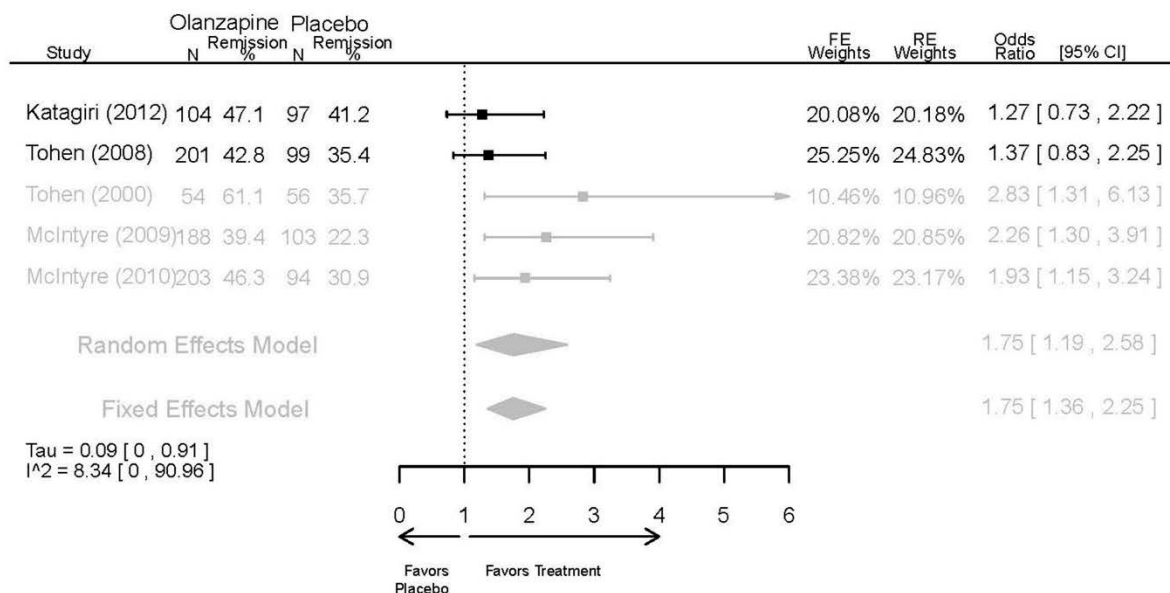
Appendix Figure E40. Olanzapine vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



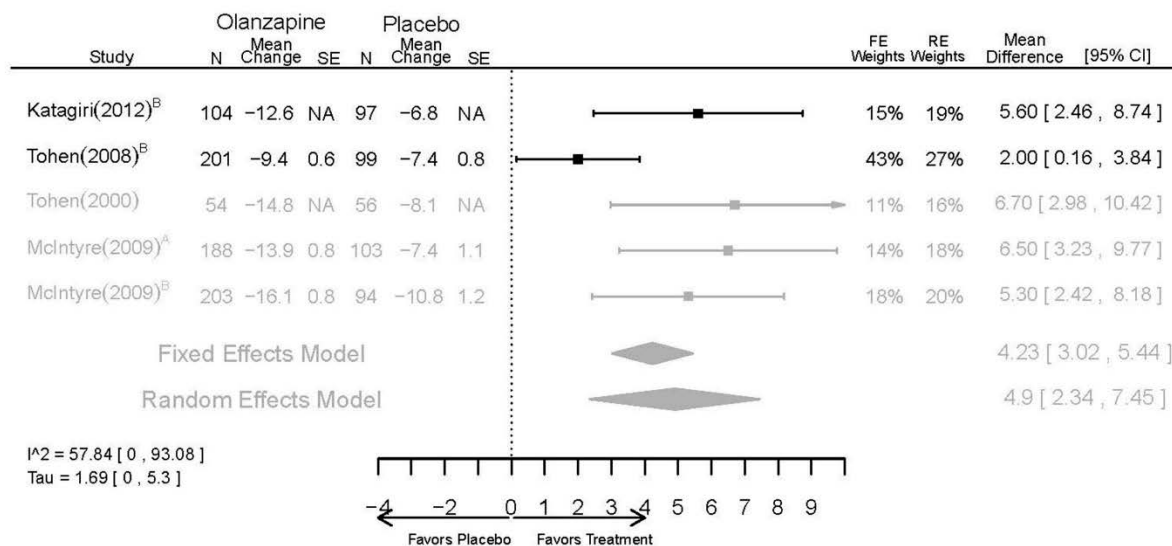
Appendix Figure E41. Olanzapine vs. placebo – remission

Odds Ratio of Remission (YMRS = 12) at 3 Weeks



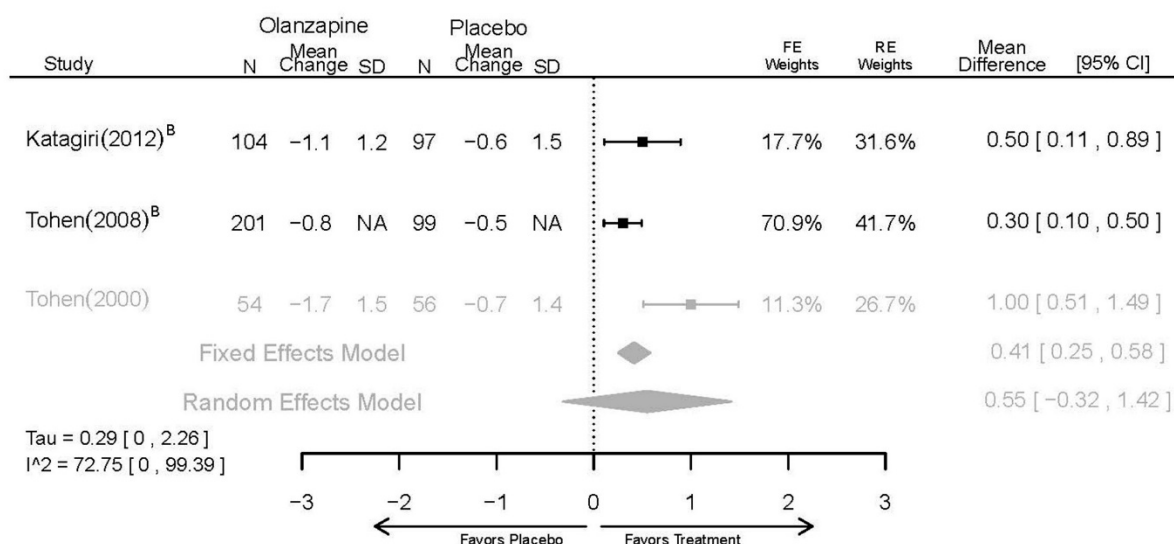
Appendix Figure E42. Olanzapine vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to 3 Weeks



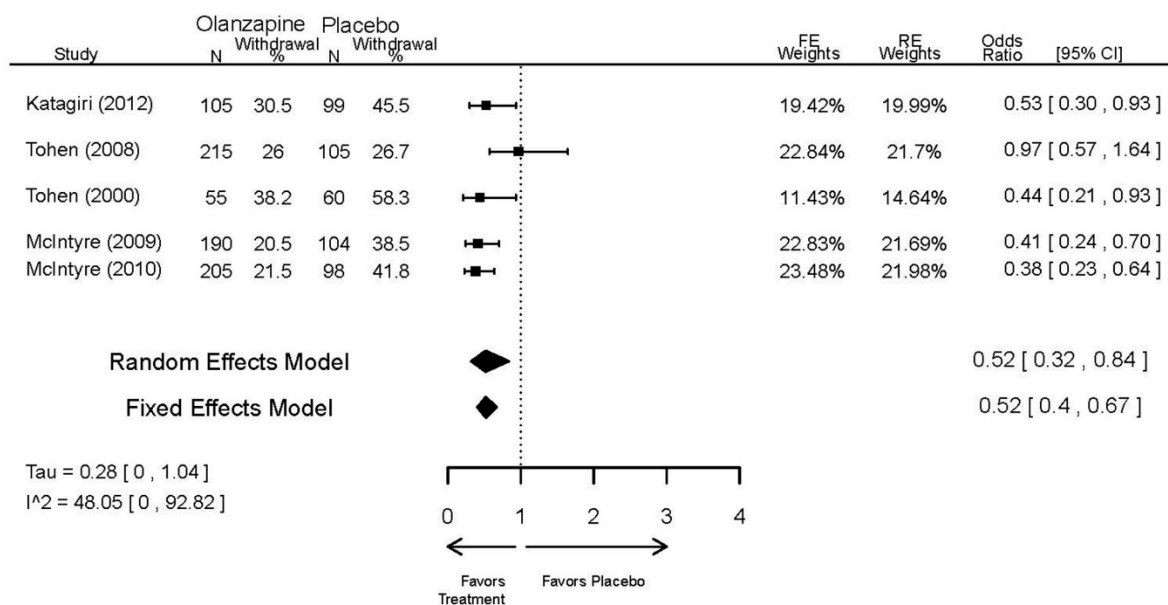
Appendix Figure E43. Olanzapine vs. placebo – CGI

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks

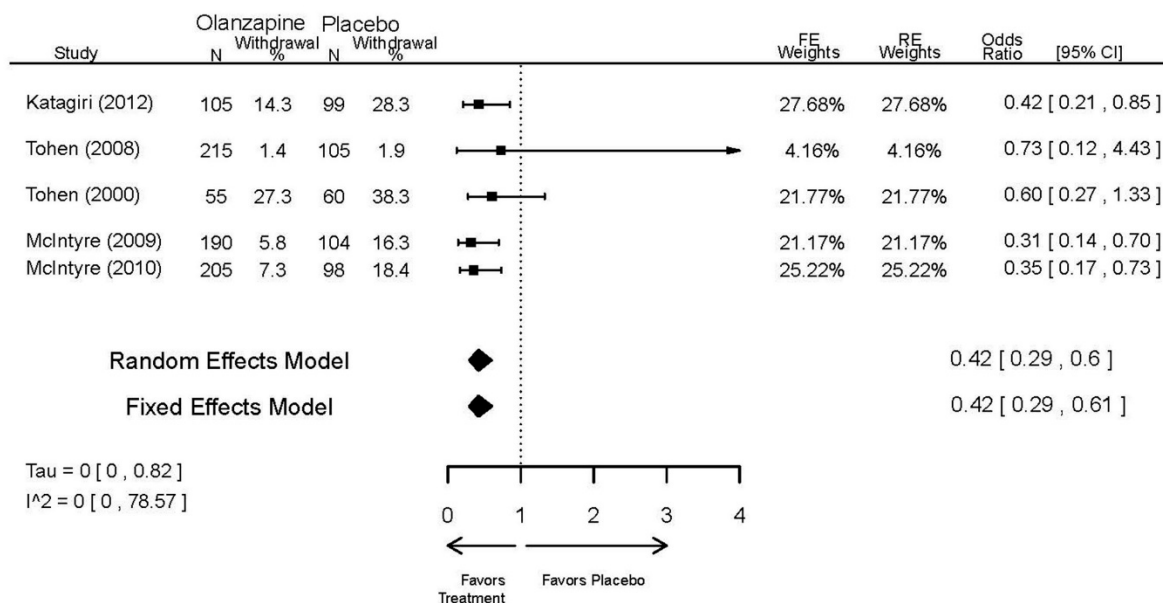


Appendix Figure E44. Olanzapine vs. placebo – overall withdrawal

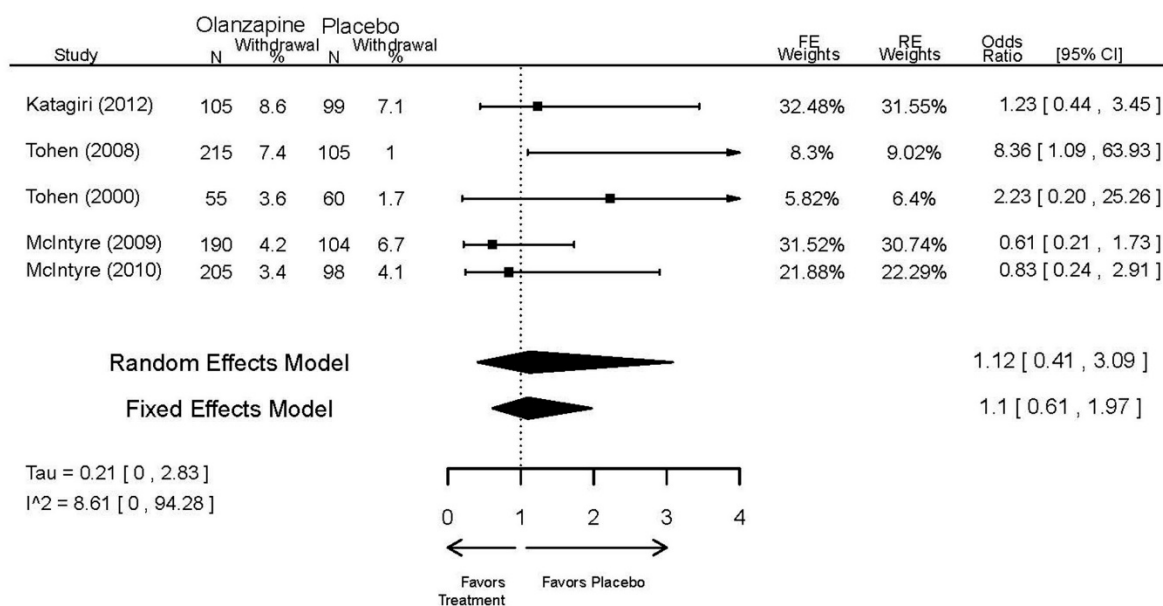
Odds Ratio of Withdrawal due to All Causes at 3 Weeks



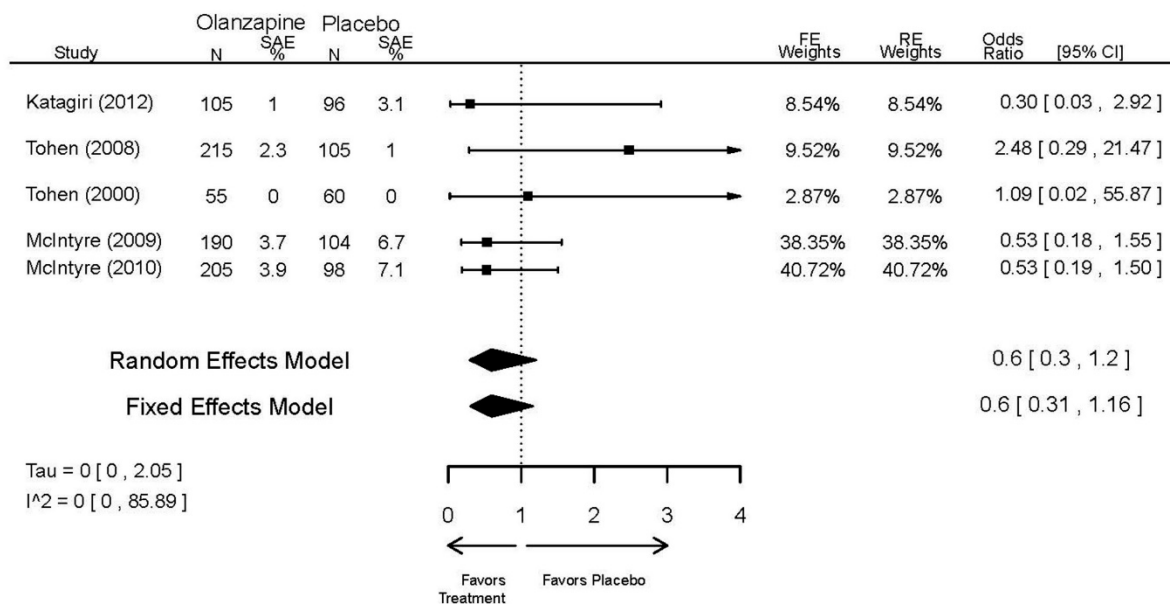
Appendix Figure E45. Olanzapine vs. placebo – withdrawal – lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



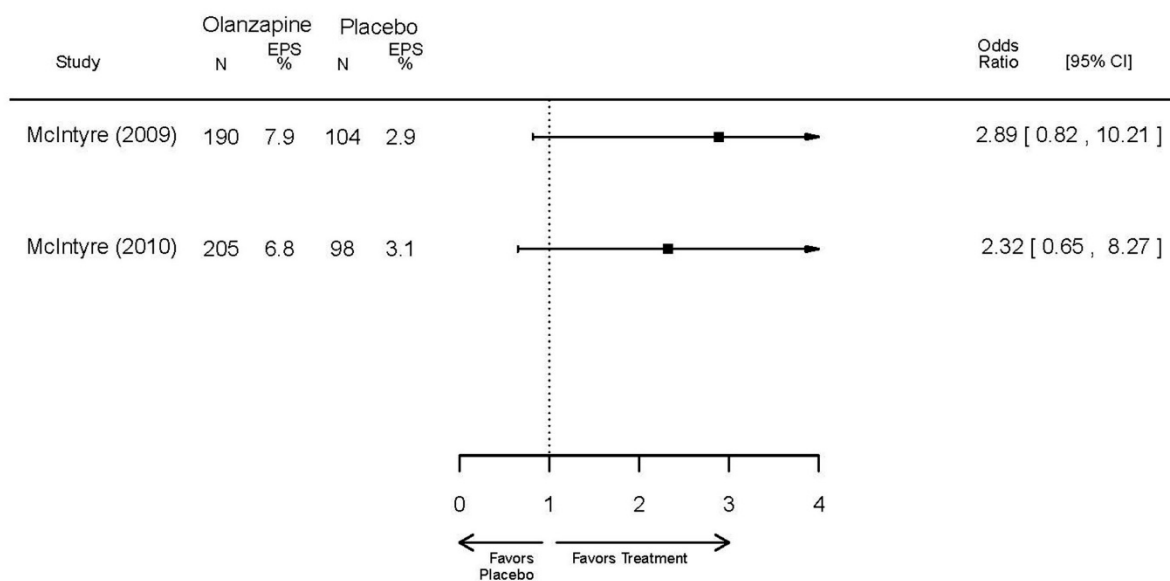
Appendix Figure E46. Olanzapine vs. placebo – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E47. Olanzapine vs. placebo – serious adverse events
Odds Ratio of Serious Adverse Events at 3 Weeks

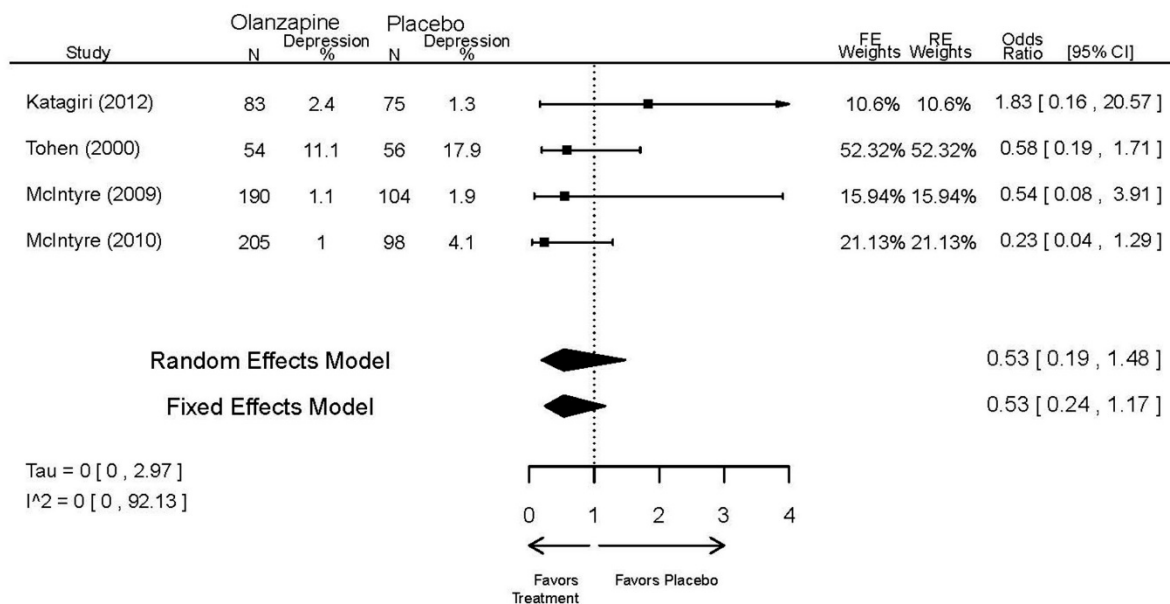


Appendix Figure E48. Olanzapine vs. placebo – EPS
Odds Ratio of Extrapyramidal Symptoms at 3 Weeks



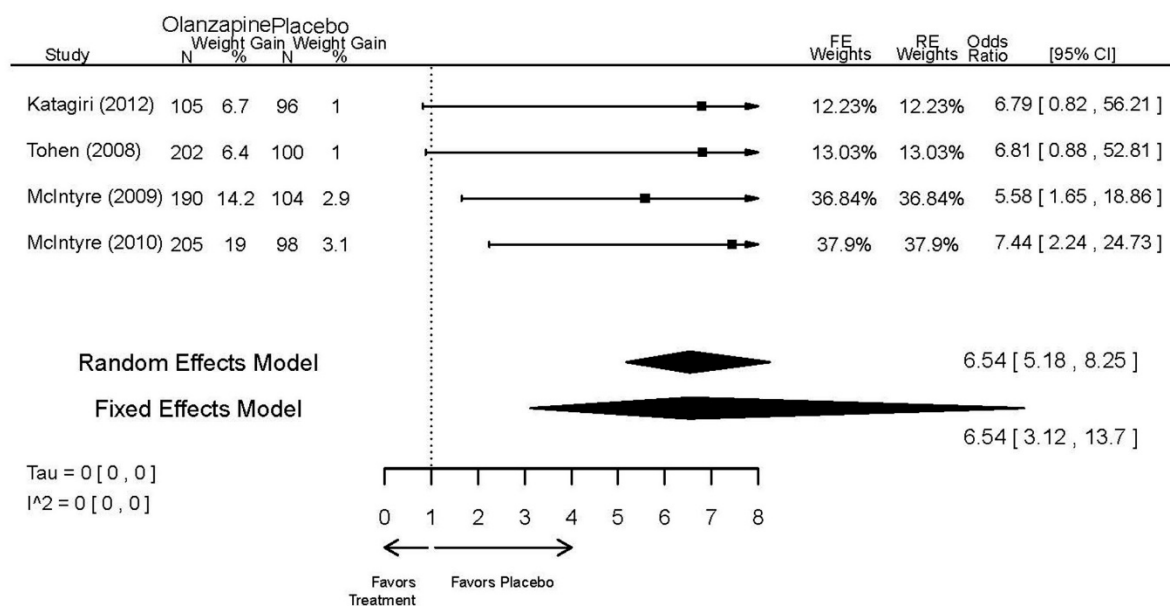
Appendix Figure E49. Olanzapine vs. placebo – emergent depression

Odds Ratio of Weight Gain of Emergent or Worsening Depression



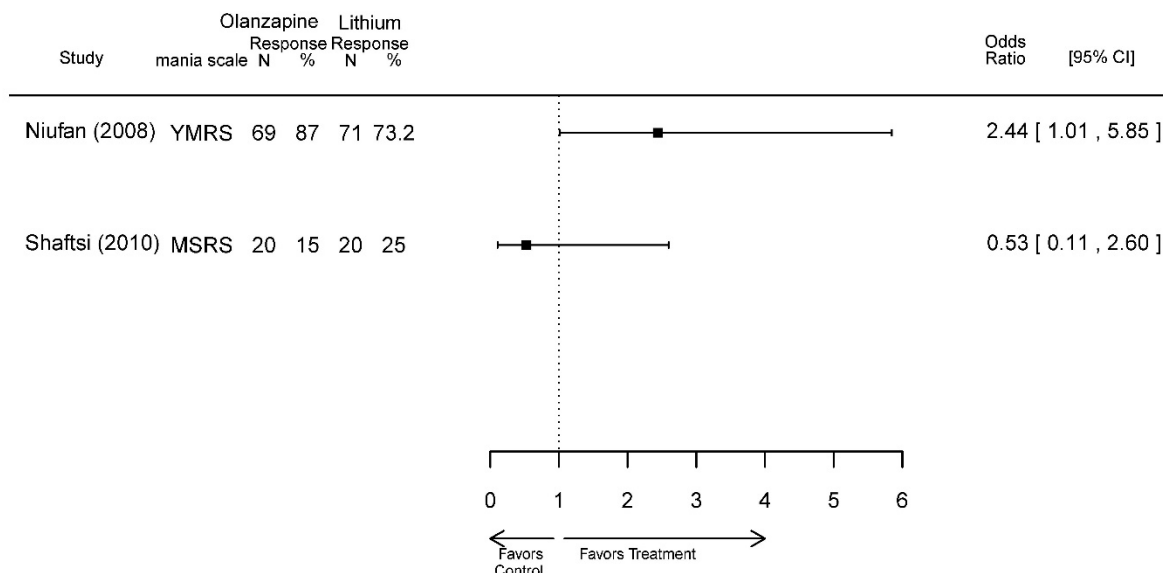
Appendix Figure E50. Olanzapine vs. placebo – weight gain

Odds Ratio of Weight Gain of at least 7% at 3 Weeks



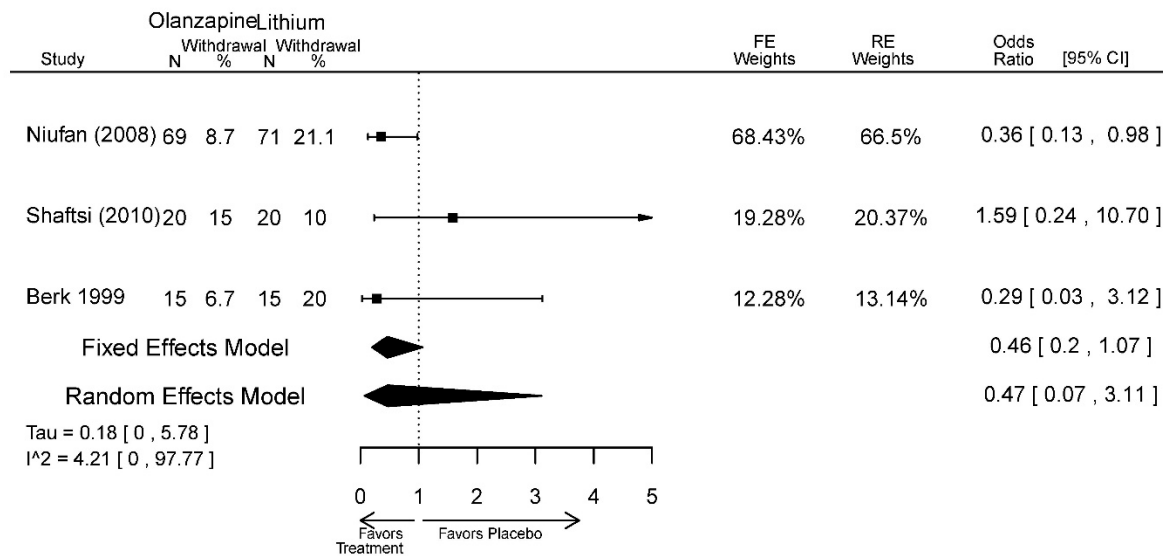
Appendix Figure E51. Olanzapine vs. lithium – response

Odds Ratio of Response (> 50% Reduction in Mania Scale) at 3 Weeks

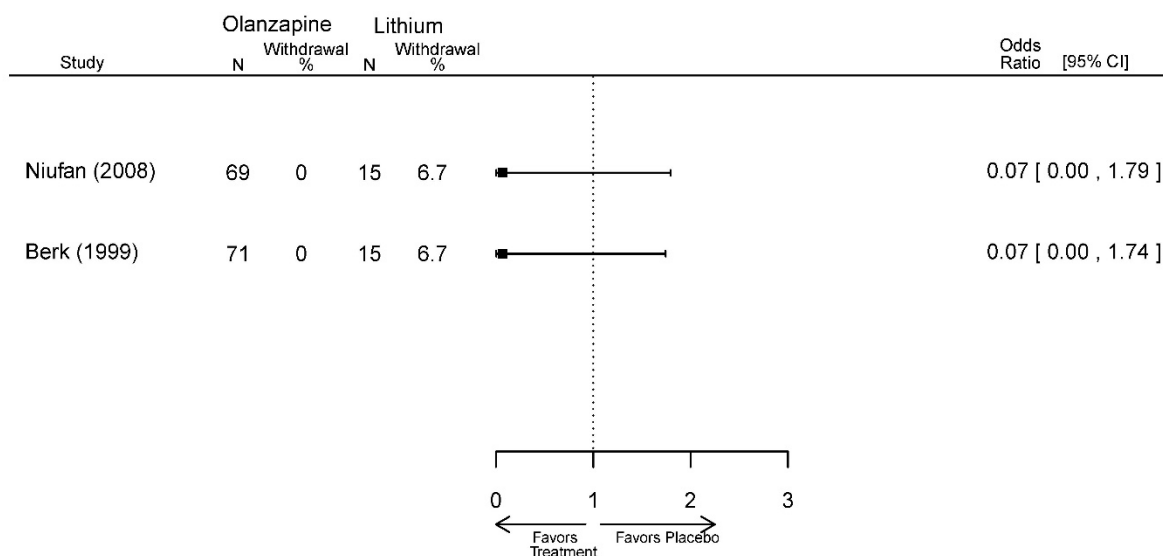


Appendix Figure E52. Olanzapine vs. lithium – overall withdrawal

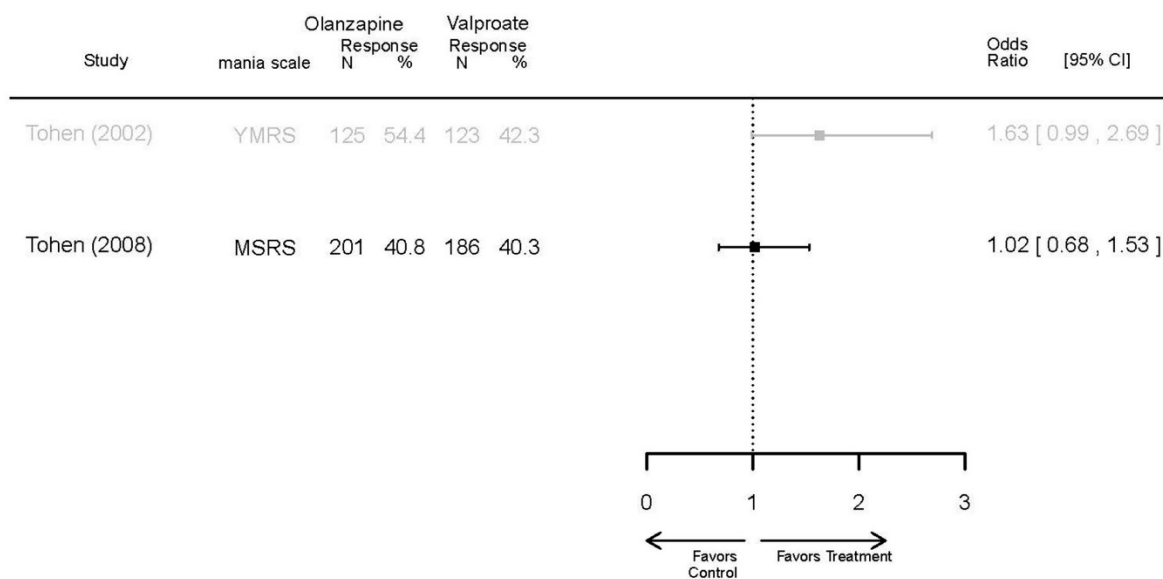
Odds Ratio of Overall Withdrawal



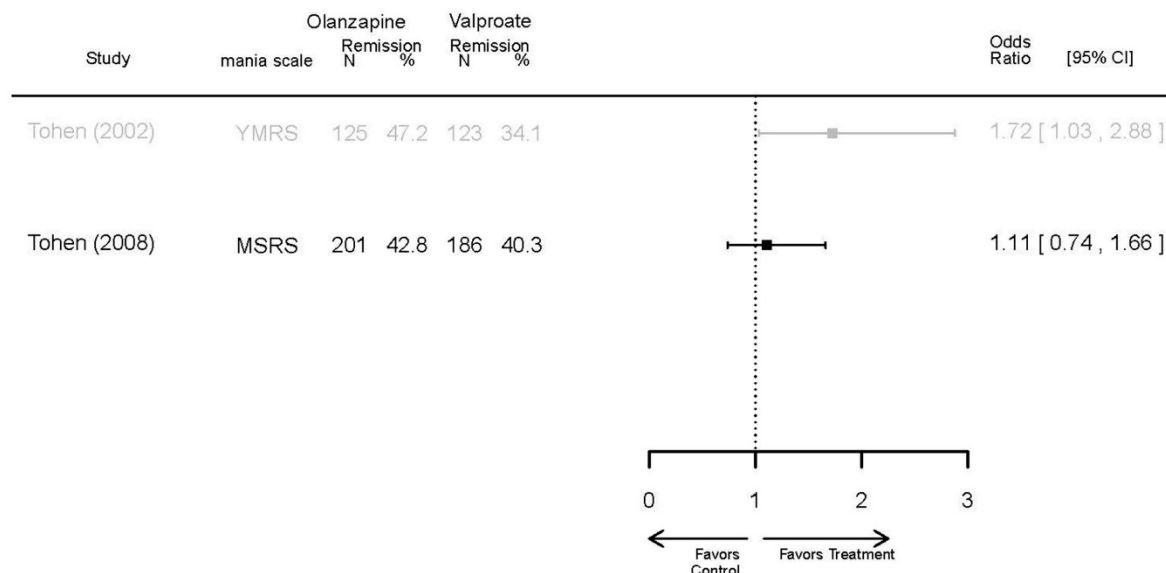
Appendix Figure E53. Olanzapine vs. lithium – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at Last Measurement



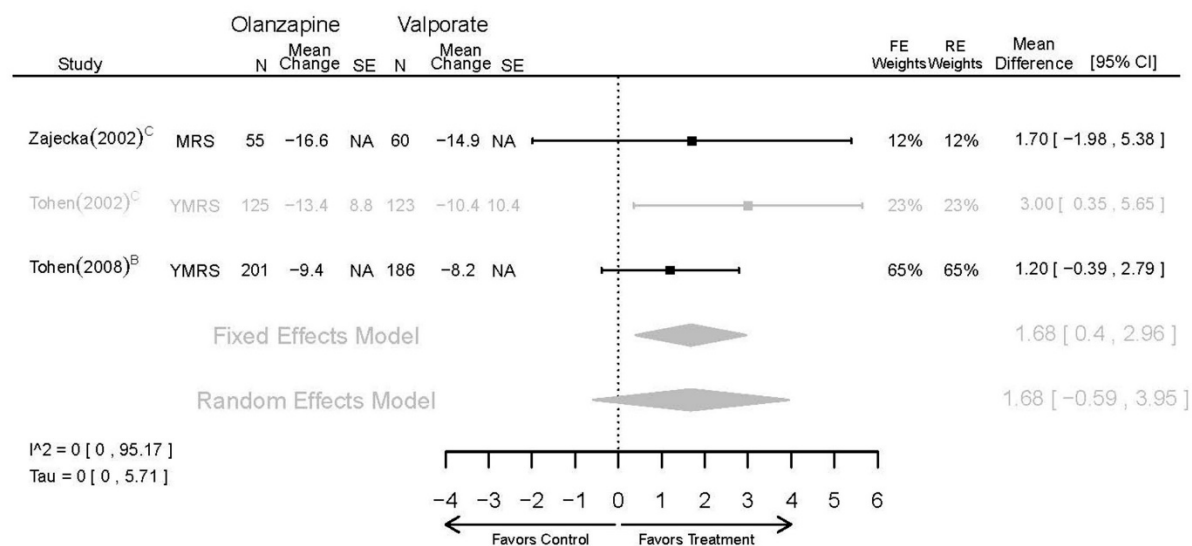
Appendix Figure E54. Olanzapine vs. divalproex/valproate – response
Odds Ratio of Response (> 50% Reduction in Mania Scale) at 3 Weeks



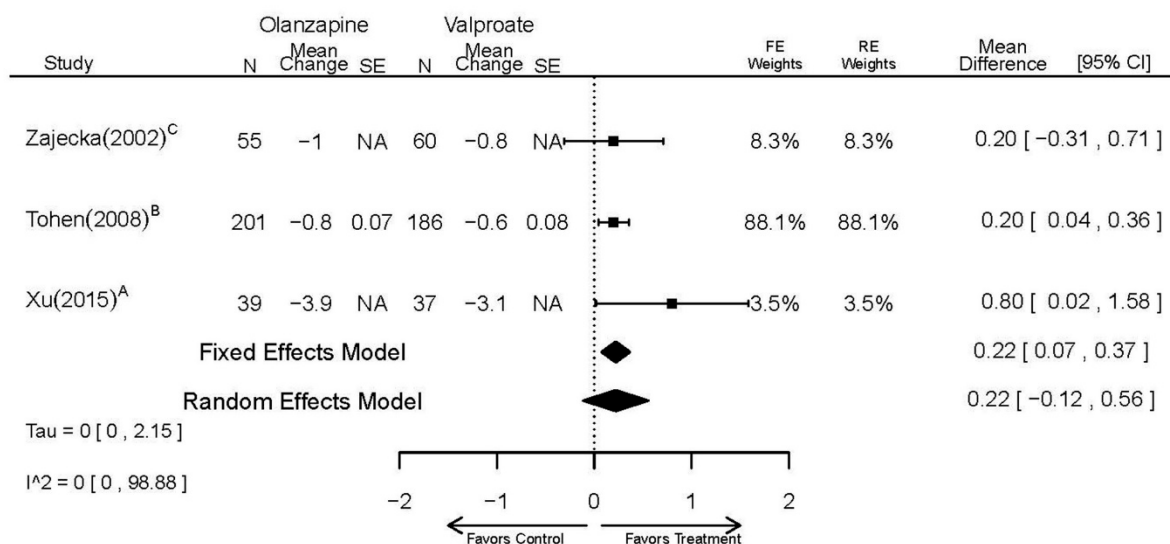
Appendix Figure E55. Olanzapine vs. divalproex/valproate – remission
Odds Ratio of Remission (YMRS 12 or less) at 3 Weeks



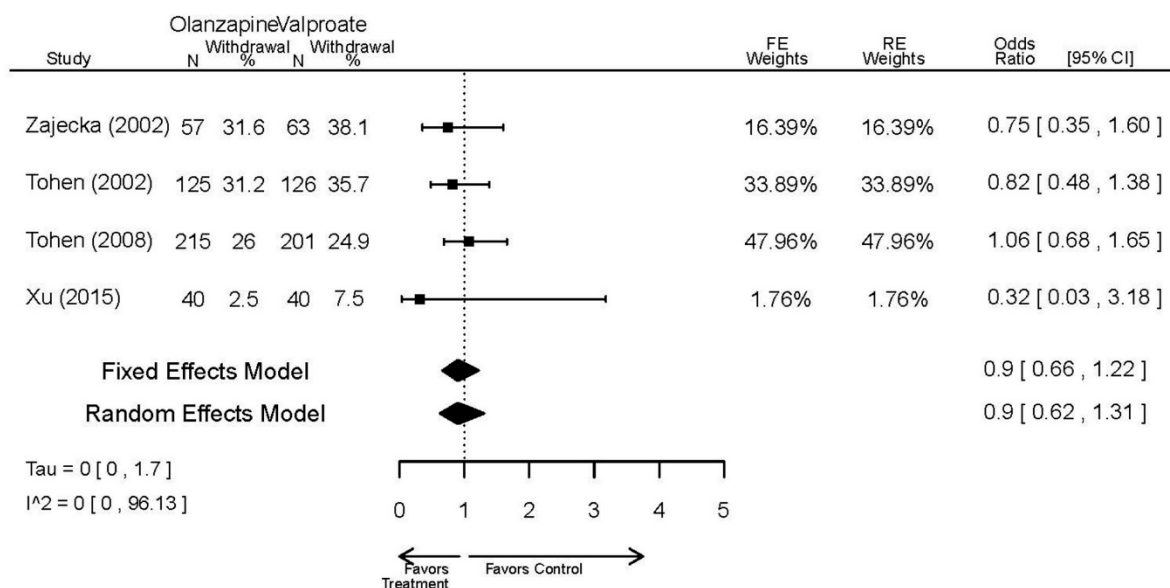
Appendix Figure E56. Olanzapine vs. divalproex/valproate – YMRS
Difference in Mean Change in YMRS
from Baseline to 3 Weeks



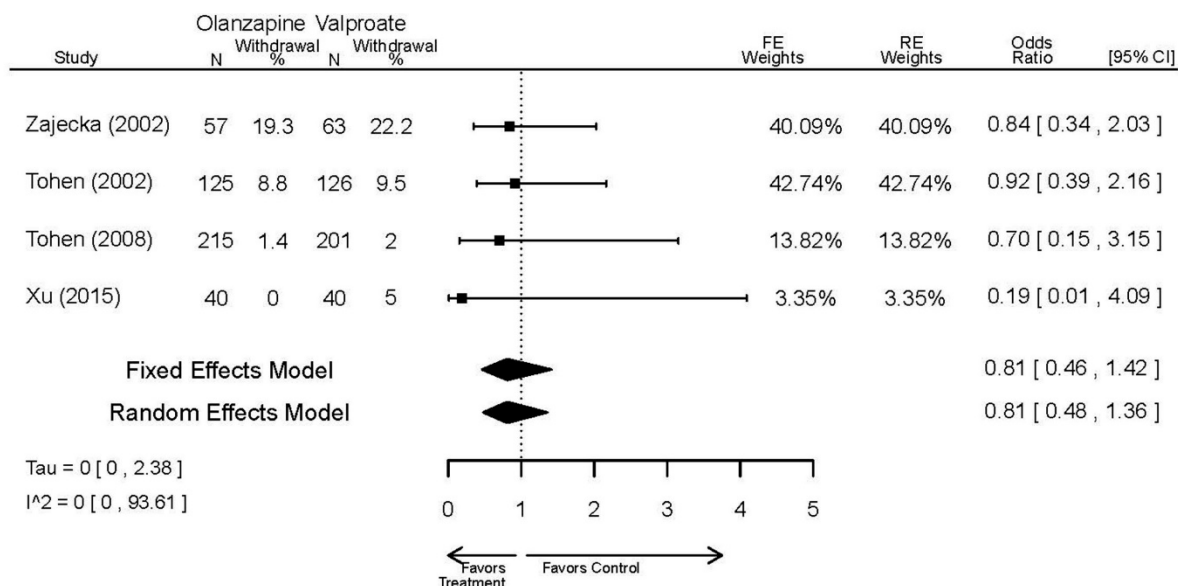
Appendix Figure E57. Olanzapine vs. divalproex/valproate – CGI
Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to 3 Weeks



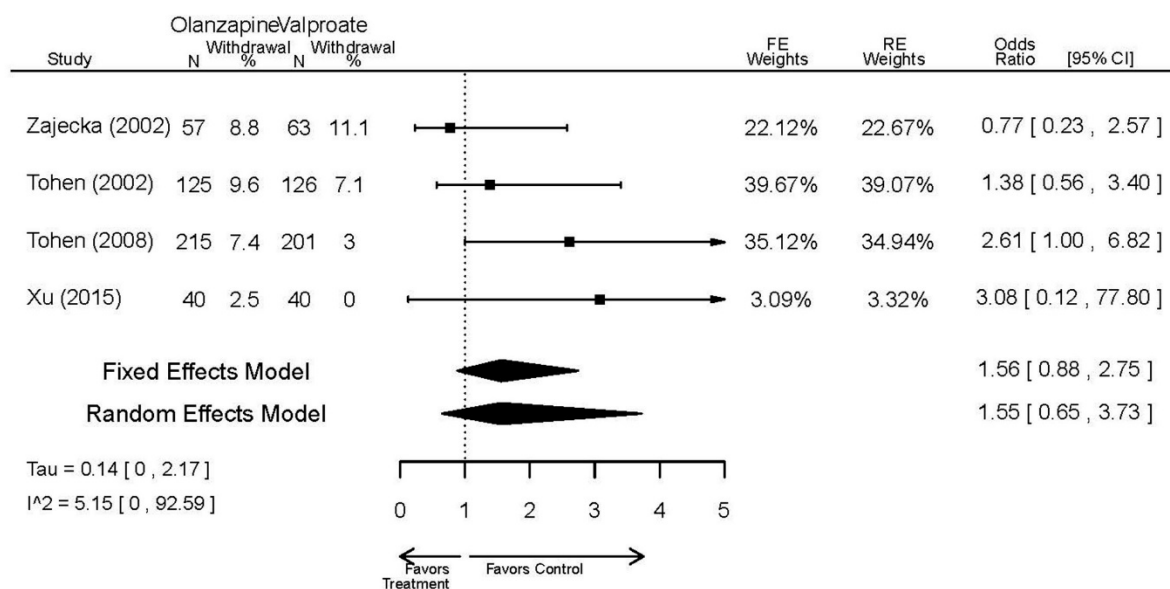
Appendix Figure E58. Olanzapine vs. divalproex/valproate – overall withdrawal
Odds Ratio of Withdrawal due to All Causes at 3 Weeks



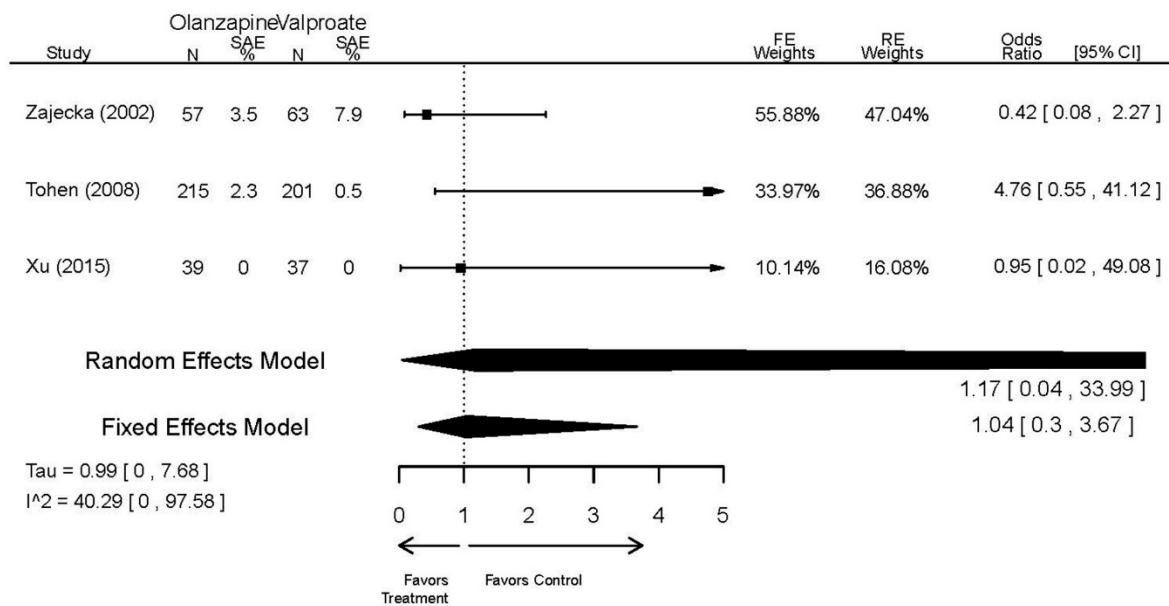
Appendix Figure E59. Olanzapine vs. divalproex/valproate – withdrawal - lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E60. Olanzapine vs. divalproex/valproate – withdrawal - adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E61. Olanzapine vs. divalproex/valproate – SAE
Odds Ratio of Serious Adverse Events at 3 Weeks



Appendix Table E23. Outcomes summary table: olanzapine versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine	Katagiri, 2012 ²⁰ 22134043 Moderate	See forest plot E40 above for response.	See forest plot E42 above for YMRS.	See forest plot E43 above for CGI.	See forest plot E44, E45, E46 above for Withdrawals.	See forest plots E47, E48, E49, E50 above for Adverse Effects.
	McIntyre, 2010 ⁸ 20096936 High	See forest plot E40 above for response.	See forest plot E42 above for YMRS.	See forest plot E43 above for CGI.	See forest plot E44, E45, E46 above for Withdrawals.	See forest plots E41, E42, E43, E44 above for Adverse Effects.
	McIntyre, 2009 ⁹ 19839993 High	See forest plot E40 above for response.	See forest plot E42 above for YMRS.	See forest plot E43 above for CGI.	See forest plot E44, E45, E46 above for Withdrawals.	See forest plots E47, E48, E49, E50 above for Adverse Effects.
	Tohen, 2008b ²⁸ 19014751	See forest plot E40 above for response.	See forest plot E42 above for YMRS.	See forest plot E43 above for CGI.	See forest plot E44, E45, E46 above for Withdrawals.	See forest plots E47, E48, E49, E50 above for Adverse Effects. <u>Suicidal Ideation</u> Olanzapine: 1 case Placebo: 0 cases
	Tohen, 2000 ²⁹ 10986547 High	See forest plot E40 above for response.	See forest plot E42 above for YMRS.	See forest plot E43 above for CGI.	See forest plot E44, E45, E46 above for Withdrawals.	See forest plots E47, E48, E49, E50 above for Adverse Effects.

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E24. Strength of evidence assessment: olanzapine versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Olanzapine vs. placebo	Response 3 wks	5 RCTs (n=1199)	Favors Olanzapine OR 1.99 (95% CI 1.29, 3.08)	Moderate	Consistent	Direct	Imprecise	Low
	Remission 3 wks	5 RCTs (n=1199)	Favors Olanzapine OR 1.75 (95% CI 1.19, 2.58)	Moderate	Consistent	Direct	Imprecise	Low
	YMRS 3 wks	5 RCTs (n=1199)	Favors Olanzapine MD 4.9 (95% CI 2.34, 7.45)	Moderate	Consistent	Direct	Imprecise	Low
	CGI-BP-S 3 wks	3 RCTs (n=611)	NS	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – Lack of Efficacy, Overall	5 RCTs (n=1199)	Favors Olanzapine	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – AE	5 RCTs (n=1199)	NS	Moderate	Consistent	Indirect	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E25. Outcomes summary: olanzapine versus active comparator for acute mania

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine vs. Haloperidol	Tohen, 2003 ²⁶ 14662554 Moderate Shi, 2002 ²⁷ 12177585 High	<u>Response</u> 6 weeks NS Olanzapine=169/234 Haloperidol=163/219 P=0.67 12 weeks NS Olanzapine=226/234 Haloperidol=206/219 P=0.42 <u>Remission</u> 6 weeks NS OR = 1.27 (95% CI 0.88, 1.84) P=0.15 12 weeks NS 1.37 (95% CI 0.94, 1.99) P=0.08	<u>YMRS</u> 6 weeks Favors Haloperidol Difference in Difference=-2.2 (95% CI -4.2, -0.2) p=0.03 12 weeks NS Difference in Difference=-0.3 (95% CI -2.0, 1.4) p=0.72	NR	<u>Overall Withdrawal</u> 12 weeks NS Olanzapine=94/234 Haloperidol=103/219 p=0.15 <u>Withdrawal due to Aes</u> 12 weeks NS Olanzapine=19/234 Haloperidol=25/219 p=0.27 <u>Withdrawal, Lack of Efficacy</u> 12 weeks NS Olanzapine=35/234 Haloperidol=33/219	<u>Normalized Weight Change</u> 12 weeks Favors Olanzapine Olanzapine=94/229 Haloperidol=34/211 p<0.001 <u>Emergent Depression</u> 12 weeks NS p=0.10 <u>Akathisia</u> 12 weeks Favors Haloperidol p<0.001

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine vs. Lithium	Niufan, 2008 ²² 17531327 Low	See forest plot above <u>Remission</u> 4 weeks Olanzapine=57/69 Lithium=50/71	<u>YMRS</u> 4 weeks Difference in Difference (SE)=-4.5 (1.8) p=0.013 Favors Olanzapine <u>CGI-BP</u> 4 weeks Difference in Difference (SE)=-0.6 (0.2) p=0.009 Favors Olanzapine MADRS 4 weeks Difference in Difference (SE)=-NS	NR	See forest plot above	<u>Severe Harms</u> 4 weeks NS Olanzapine=0/69 Lithium=0/71 <u>EP Symptoms</u> 4 weeks NS Olanzapine=1/69 Lithium=2/71 <u>Normalized Weight Change</u> 4 weeks NS Olanzapine=11/69 Lithium=2/71 <u>Emergent Mood Episodes</u> 4 weeks NS Olanzapine=0/69 Lithium=0/71

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Shafiti, 2010 ³³ 19740546 Moderate	See forest plot above	<u>YMRS</u> 3 weeks Favors Lithium Frequency, Difference in Difference= -12.7 (95% CI -19.0, -6.4) P<0.001 Intensity, Difference in Difference= -8.0 (95% CI -13.9, -2.1) P=0.009 <u>CGI, Severity of Illness</u> 3 weeks NS Difference in Difference= -0.1	NR	See forest plot above	NR
	Berk, 1999 ³⁰ 10565800 High	NR	<u>Mania Scale</u> 4 weeks NS Difference in Difference=3.1 P=0.32 <u>CGI-BP</u> 4 weeks Favors Olanzapine Difference in Difference=0.5 P=0.03	NR	See forest plot above <u>Withdrawal, Lack of Efficacy</u> 4 weeks NS Olanzapine=1/15 Lithium=0/15	NR

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine vs. Risperidone	Perlis, 2006 ²⁴ 17196055 High	<u>Response</u> 3 weeks NS OR = 1.12 (95% CI 0.72, 1.75) P = 0.65 <u>Remission</u> 3 weeks NS OR = 1.57 (95% CI 1.0, 2.51) P = 0.06	<u>YMRS</u> 3 weeks NS Olanzapine=-15.0 Risperidone=-16.6	<u>CGI-BP</u> 3 weeks NS Olanzapine=-1.6 Risperidone=-1.5	<u>Overall Withdrawal</u> 3 weeks Favors Risperidone Olanzapine=35/165 Risperidone=54/164 OR = 0.55 (95% CI 0.33, 0.90) P = 0.019 <u>Withdrawal due to Aes</u> 3 weeks NS Olanzapine=9/165 Risperidone=14/164 OR = 0.62 (95% CI 0.25, 1.48) P = 0.29 <u>Withdrawal, Lack of Efficacy</u> 3 weeks NS Olanzapine=7/165 Risperidone=7/164	<u>EP Symptoms</u> 3 weeks NS Olanzapine=23/165 Risperidone=37/164 P=0.06 <u>Emergent Depression</u> 3 weeks Olanzapine=2/165 <u>Akathisia</u> 3 weeks NS Olanzapine=13/165 Risperidone=17/164 P=0.45 <u>Suicidality</u> 3 weeks 3 patients in the Risperidone arm were discontinued for suicidality
Olanzapine vs. Divalproex/ Valproate	Xu, 2015 ¹⁹ 26060401 Low	NR	YMRS % decrease 4 weeks Olanzapine 75.2 (15.08) Valproate 55.11 (5.72) Favors Olanzapine p<0.01	NR	See forest plot above	See forest plot above

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Tohen, 2008 ²³ 19014751 Low	See forest plot above	See forest plot above	NR	See forest plot above	<u>Normalized Weight Change</u> 4 weeks Olanzapine=13/202 Divalproex=5/188 <u>Suicide Ideation</u> 3 weeks NS Olanzapine=1/215 Divalproex=0/201 12 weeks NS Olanzapine=2/215 Divalproex=1/201 Weight gain >7% Favored Divalproex p=0.002
	Zajecka, 2002 ³⁵ 12523875 Revicki, 2003 ²⁵ 12716270 Moderate	NR	See forest plot above <u>YMRS</u> 4 weeks Favors Olanzapine % Reduction (SD) Olanzapine: 75.2% (15.1%) Divalproex: 55.2% (5.7%) P<0.001	NR	See forest plot above	See forest plot above <u>Emergent Depression</u> 4 weeks NS Olanzapine: 1/57 Divalproex: 1/63 <u>Deaths</u> 4 weeks 1 Olanzapine-treated patient died from diabetic ketoacidosis
	Tohen, 2002 ²⁸ 12042191 High	See forest plot above	See forest plot above	NR	See forest plot above	See forest plot above EPS No difference between groups

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E26. Strength of evidence assessment: olanzapine versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Olanzapine vs. haloperidol	Response 6,12 wks Remission 6,12 wks YMRS 6, 12 wks Withdrawals	1 RCT (n=453)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. Lithium	Response 4 wks	2 RCTs (n=180)	See forest plot above	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	YMRS 4 wks CGI 4 wks Withdrawal	3 RCT (n=210)	See table above	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Olanzapine vs. Risperidone	Response 3 wk Remission 3 wk YMRS 3 wk CGI Withdrawals	1 RCT (n=329)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. Divalproex/ Valproate	Response Remission	2 RCTs (n=635)	NS	Moderate	Consistent	Direct	Imprecise	Low
	YMRS	3 RCTs (n=750)	NS	Moderate	Consistent	Direct	Imprecise	Low
	CGI	3 RCTs (n=578)	NS	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawals	4 RCTs (n=867)	NS	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an

assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 6. Quetiapine for Acute Mania

Appendix Table E27. Characteristics of eligible studies: quetiapine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Cutler, 2011 ³⁶ RCT Multisite US Industry RoB Low 22054797	N = 316 Mean Age 41 Female 40% White 47% BP-I 100% Inpatient (days 1-4, minimum) Outpatient (at inspectors discretion)	Mania; YMRS \geq 20 overall, YMRS \geq 4 on at least 2 of 4 specified mania domains, and CGI- BP-S \geq 4 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Labs/Other Conditions	Quetiapine ER 300-800 mg/day (603.8 mg/day mean)	Placebo	3 Weeks	CGI-BP-S CGI-BP-C MADRS Remission (YMRS \leq 12) Response (YMRS 50% decrease) YMRS Withdrawal 29%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
McElroy, 2010 ³⁷ Singlesite US Industry RoB Low 19963274	N = 41 Mean Age 35 Female 51% White 69% BP-I 74% BP-II 21% BP-NOS 5% Outpatient	Mild to moderate hypomania or mild mania; CGI-BP ≥3 AND <5 Substance Abuse Other Mental Health Neurological Disorders Pregnant Nursing Labs/Other Conditions	Quetiapine 50-800 mg/day (232 mg/day mean)	Placebo	8 weeks	CGI-BP-S GAF HAM-A IDS Remission (YMRS ≤7 at week 8, CGI-BP Overall ≤2 at week 8, Improvement or no change in IDS score from baseline to week 8) Response (YMRS 50% decrease) YMRS Withdrawal 36%
Vieta, 2010 ¹⁸ RCT Multisite 3 continents Industry RoB High 20565430	N = 493 Mean Age 39 Female 42% Race NR BP-I 100% Inpatient (1 week) Outpatient (weeks 2- 3, subject to inspector discretion)	Mania; YMRS ≥ 20 First Manic Episode Schizoaffective Substance Abuse Neurological Disorders	Quetiapine 400-800 mg/day (600 mg/day mean)	Placebo (Paliperidone arm discussed in Other Drugs section)	3 weeks	Duration of Episode YMRS GAF PANSS CGI-BP-S SAS AIMS MADRS Withdrawal 28%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Li, 2008 ³⁸ RCT Multisite China Industry RoB Moderate 18028587	N = 154 Mean Age 33 Female 53% Race NR Diagnosis NR Inpatient (weeks 1-2) Outpatient (week 2-4, subject to inspector discretion)	Mania; YMRS ≥ 20 Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Quetiapine 100-800 mg/day (648.2 mg/day mean)	Lithium 250-2000 mg/day (target serum level 0.6-1.2 mmol/L) (0.80 mmol/L average)	4 weeks	MADRS PANSS Remission (various definitions) Response (YMRS 50% decrease) Weight YMRS Withdrawal 12%
Bowden, 2005 ³⁹ RCT Multisite 2 Continents Industry RoB High 15669897	N = 302 Mean Age 39 Female 24% Race NR BP-I 100% Inpatient	Mania; YMRS ≥ 20 including score of at least 4 on 2 of the 4 double- weighted items (irritability, speech, content, and disruptive/aggressive behavior), CGI ≥ 4 First Manic Episode Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Quetiapine 100-800mg/day	Placebo Lithium 0.6-1.4 mEq/L (mean 0.80 mEq/L)	12 weeks	CGI-BP-S Overall Global Assessment Scale (GAS) MADRS PANSS (positive) Remission (YMRS≤12) Response (50% decrease in YMRS) YMRS Withdrawal 48%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-

related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table E28. Summary risk of bias assessments: quetiapine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Quetiapine	McElroy, 2010 ³⁷ Industry 19963274	Moderate	No specific sources of bias identified. Attrition rate 36%
	Cutler, 2011 ³⁶ Industry 22054797	Low	Blinding not described. No other sources of bias identified.
	Vieta, 2010 ¹⁸ Industry 20565430	High	Blinding not described; large dropout in placebo group (41%).
	Li, 2008 ³⁸ Industry 18028587	Moderate	Randomization and blinding procedure not described.
	Bowden, 2005 ³⁹ Industry 15669897	High	Randomization and blinding procedure not described; >50% dropout in placebo group at day 84; 33% at 3 weeks
	McIntyre, 2005 ¹⁴ Industry 16139175	Moderate	Dropout rate for quetiapine and placebo in 30%-40% range, lacks some core information on how allocation was concealed and blinding of treatment staff and raters was maintained. Author notes may be underpowered for quetiapine vs. haloperidol comparison.

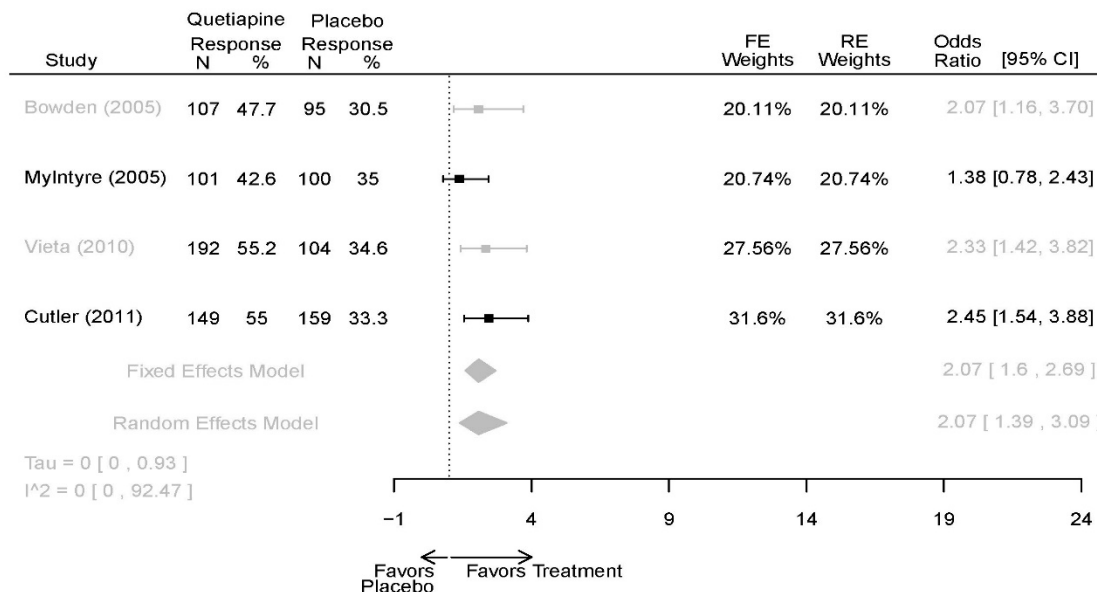
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Quetiapine Forest Plots

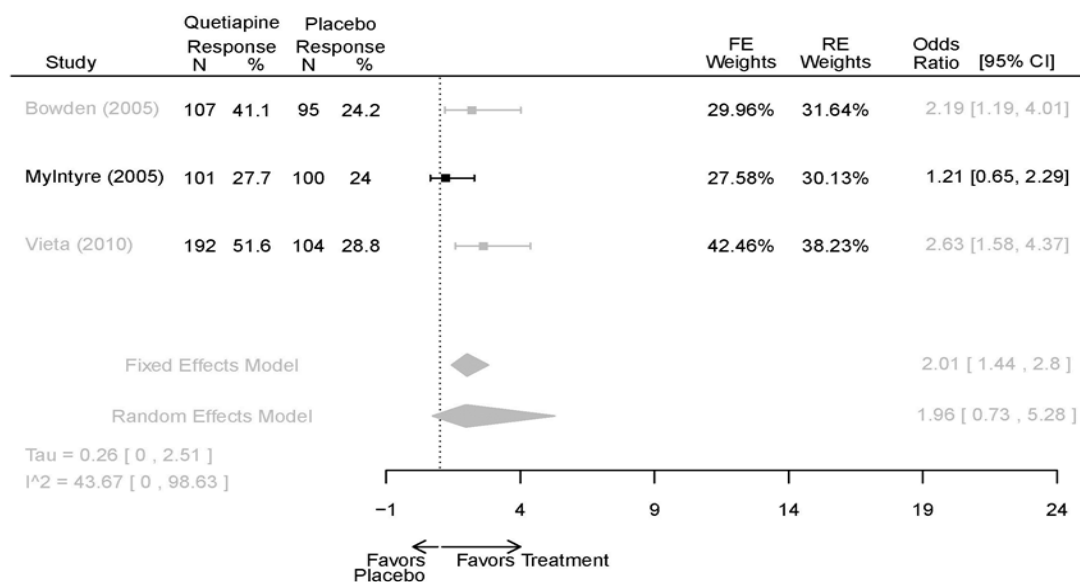
Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

Appendix Figure E62. Quetiapine vs. placebo – response

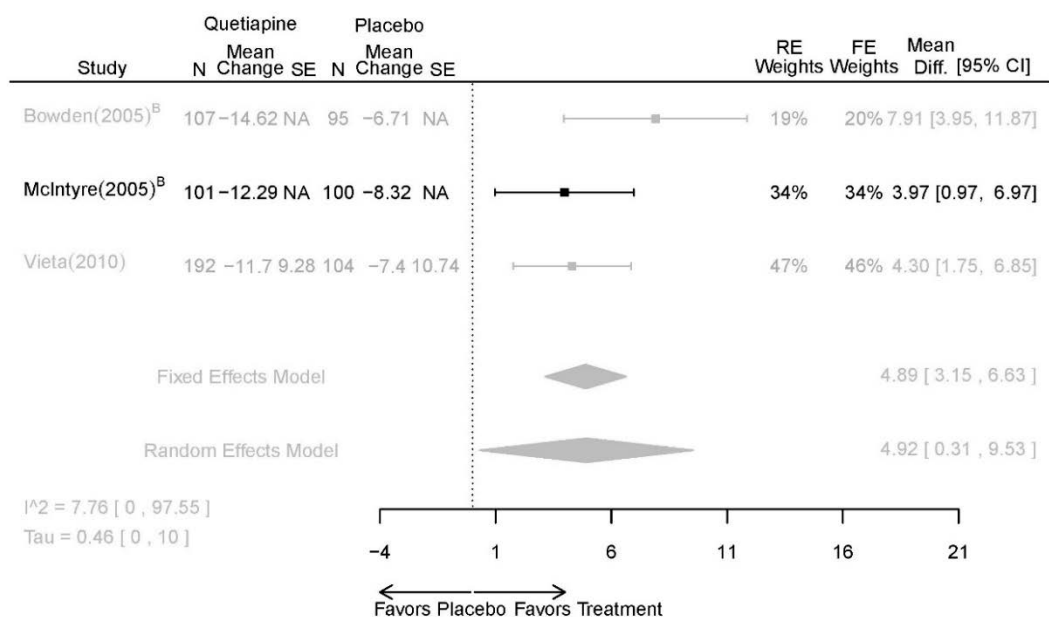
Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



Appendix Figure E63. Quetiapine vs. placebo – remission
Odds Ratio of Remission (YMRS ≤ 12) at 3 Weeks

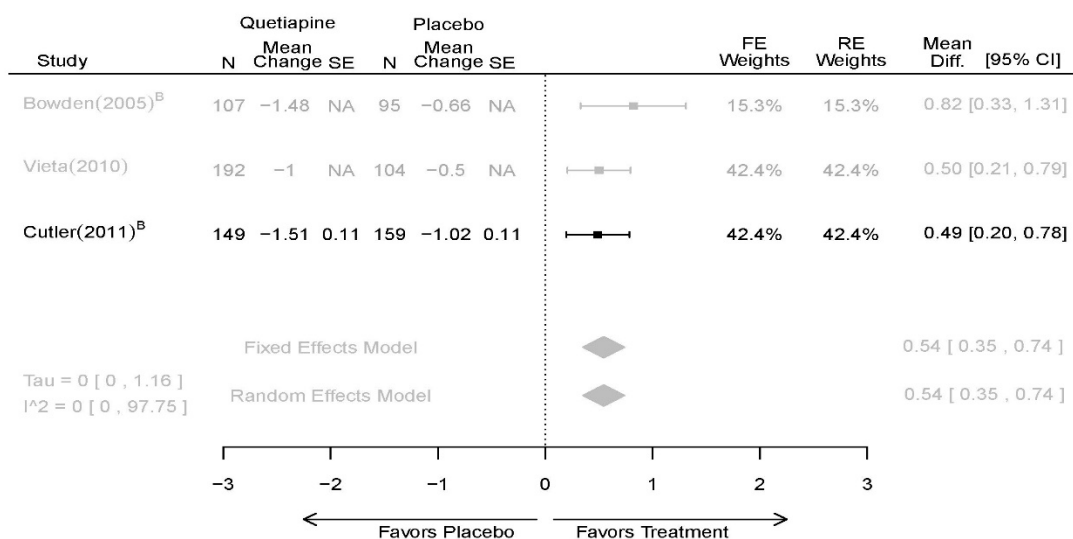


Appendix Figure E64. Quetiapine vs. placebo – YMRS
Difference in Mean Change in YMRS from Baseline to 3 Weeks



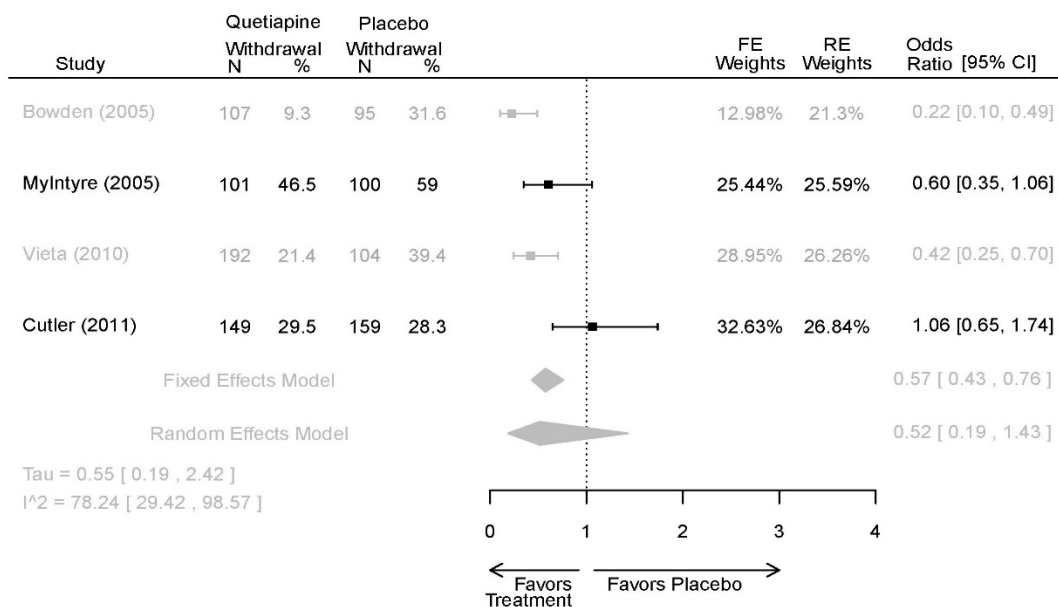
Appendix Figure E65. Quetiapine vs. placebo – CGI

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks

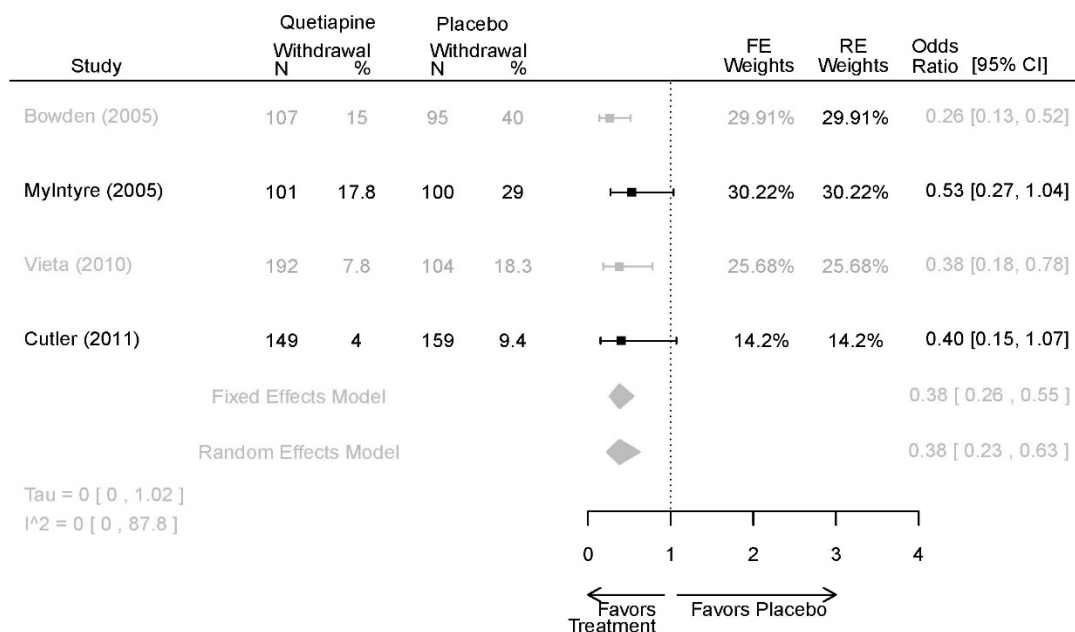


Appendix Figure E66. Quetiapine vs. placebo – overall withdrawal

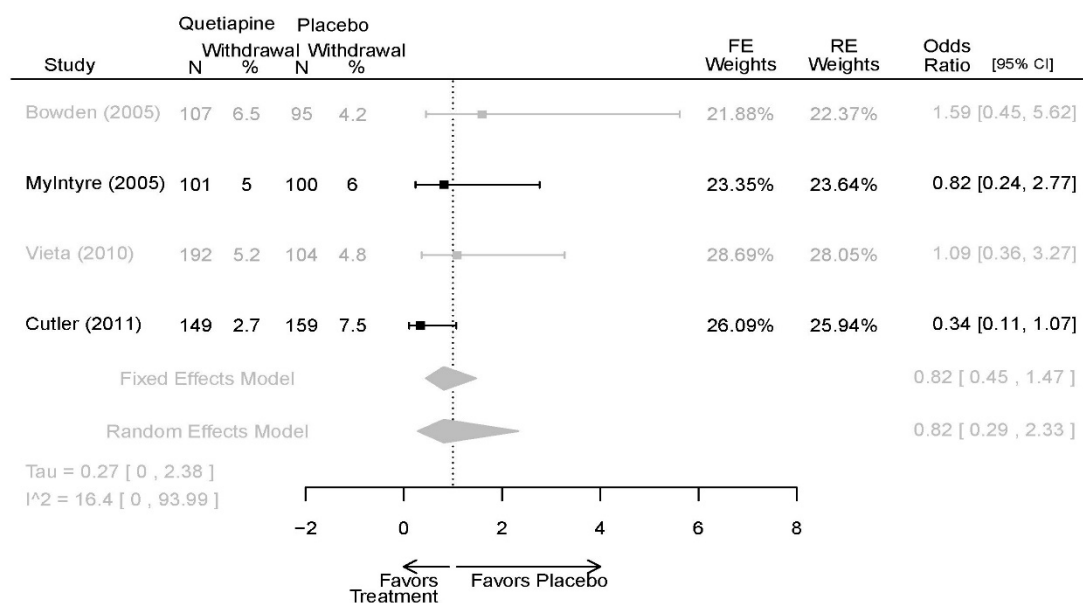
Odds Ratio of Overall Withdrawal



Appendix Figure E67. Quetiapine vs. placebo – withdrawal lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E68. Quetiapine vs. placebo – withdrawal adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Table E29. Outcomes summary: quetiapine versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Quetiapine	McElroy, 2010 ³⁷ 19963274 Moderate	<u>Response</u> 8 weeks Completers only reported <u>Remission</u> 8 weeks Completers only reported	<u>YMRS</u> 8 weeks Regression model NS (p=0.06)	<u>CGI</u> 8 weeks Regression model Favors Quetiapine (p<0.001) GAF 8 weeks Regression model NS	<u>Overall Withdrawal</u> Quetiapine 6/21 Placebo 8/20 <u>Withdrawal Lack of efficacy</u> Quetiapine 0/21 Placebo 2/20 <u>Withdrawal AE</u> Quetiapine 2/21 Placebo 1/20	<u>Serious Adverse Events</u> 3 weeks 3 placebo – 2 suicide, 1 death, 1 quetiapine – suicide attempt <u>Deaths</u> 3 weeks 1 placebo <u>EPS</u> 3 weeks 3.8% placebo 6.6% Quetiapine
	Cutler, 2011 ³⁶ 22054797 Low	See forest plot E62 above for Response.	See forest plot E64 above for YMRS.	See forest plot E65 above for CGI	See forest plots E66, E67, E68 above for withdrawals	<u>SAE</u> Quetiapine 4.0% Placebo 8.1% <u>Deaths</u> 3 placebo – 2 suicide, 1 death, 1 quetiapine – suicide attempt <u>EPS</u> 3 weeks 3.8% placebo 6.6% Quetiapine
	Vieta, 2010 ¹⁸ 20565430 High	See forest plot E562 above for Response.	See forest plot E64 above for YMRS.	See forest plot E65 above for CGI	See forest plots E66, E67, E68 above for withdrawals	<u>SAE</u> Reported no difference 1 suicide reported <u>Akathisia</u> Quetiapine 6 (3%) Placebo 3 (3%)

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Bowden, 2005 ³⁹ 15669897 High	See forest plot E62 above for Response.	See forest plot E64 above for YMRS.	See forest plot E65 above for CGI	See forest plots E66, E67, E68 above for withdrawals	<u>SAE</u> None reported <u>EPS</u> Reported no difference <u>Weight gain >7%</u> Quetiapine more frequent (p=0.008)
	McIntyre, 2005 ¹⁴ 16139175 Moderate	See forest plot E62 above for Response.	<u>YMRS</u> 3 weeks ANCOVA model Favors Quetiapine p=.01 Results sustained at 12 weeks	CGI 3 weeks ANCOVA model Favors Quetiapine (p<0.05) Results sustained at 12 weeks	See forest plots E66, E67, E68 above for withdrawals	<u>SAE</u> None reported <u>EPS</u> Quetiapine 13 (12.7%) Placebo 16 (15.8%) NS <u>Weight gain >7%</u> Quetiapine 12.8% Placebo 4% NS

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E30. Strength of evidence assessment: quetiapine versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Quetiapine vs. placebo	Response 3 wks	4 RCT (n=1,007)	Favors Quetiapine OR 2.07 (95% CI 1.39, 3.09)	Moderate	Consistent	Direct	Imprecise	Low
	Remission 3 wks	3 RCT (n=699)	NS	High	Consistent	Direct	Imprecise	Insufficient
	YRMS 3 wks	5 RCT (n=699 forest plot, 1439 total)	Favors Quetiapine MD 4.92 (95% CI 0.31, 9.53)	Moderate	Inconsistent	Direct	Imprecise	Low
	CGI-BP-S 3 wk	5 RCT (n=806 forest plot, 1439 total)	Favors Quetiapine Mean Difference 0.54 (95% CI 0.35, 0.74)	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – AE, Overall	4 RCT (n=1,007)	NS	Moderate	Consistent	Indirect	Imprecise	Insufficient
	Withdrawal –Lack of Efficacy	4 RCT (n=1,007)	Favors Quetiapine Mean Difference 0.38 (95% CI 0.23, 0.63)	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E31. Outcomes summary: quetiapine versus active comparator for acute mania

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Quetiapine vs. haloperidol	McIntyre, 2005 ¹⁶ 16139175 Moderate	<u>Response</u> 3 weeks Quetiapine 42.6% Haloperidol 56.1% NS <u>Remission</u> 3 weeks Quetiapine 27.7% Haloperidol 36.7% NS	<u>YMRS Change</u> 3 week Quetiapine -12.29 Haloperidol -15.71 No Statistical Tests reported	<u>CGI-BP-S Change</u> 3 week Quetiapine -1.02 Haloperidol -1.33 No Statistical Tests reported <u>GAS</u> 12 weeks Favors quetiapine against placebo p < .001 12 weeks Favors haloperidol against placebo p < .001	NR <u>Overall Withdrawal</u> Quetiapine 55/102 Haloperidol 45/99 <u>Withdrawal Lack of Efficacy</u> Quetiapine 18/102 Haloperidol 10/99 <u>Withdrawal AE</u> Quetiapine 5/102 Haloperidol 10/99	<u>Serious Adverse Events</u> 12 weeks 0 in both arms <u>Deaths</u> 12 weeks 0 in both arms <u>EPS</u> 12 weeks 12.7% Quetiapine 59.6% Haloperidol
Quetiapine vs. lithium	Bowden, 2005 15669897	<u>Response</u> 12 weeks Quetiapine 72.0% Lithium 75.5% No Statistical Tests reported <u>Remission</u> 12 weeks Quetiapine 69.2% Lithium 72.4% No Statistical Tests reported	<u>YMRS Change</u> 12 weeks Quetiapine -20.28 Lithium -20.76 NS	<u>CGI-BP-S Change</u> 12 weeks Quetiapine -2.20 Lithium -2.18 No Statistical Tests reported <u>GAS Change</u> 12 weeks Quetiapine 26.35 Lithium NR No Statistical Tests reported	NR	<u>Serious Adverse Events</u> 12 weeks 0 in both arms <u>Deaths</u> 12 weeks 0 in both arms <u>EPS</u> 12 weeks 9.3% placebo 13.1% Quetiapine NR Lithium

Comparison	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Li, 2008 18028587 Moderate	<u>Response</u> 4 weeks Favors quetiapine Quetiapine 77.9% Lithium 59.7% p=0.013 <u>Remission</u> 4 weeks Favors quetiapine Quetiapine 70.1% Lithium 48.1% p=0.007	<u>YMRS Change</u> 4 weeks Quetiapine -18.2 (10.4) Lithium -15.9 (12.2) NS	NR	NR	<u>Serious Adverse Events</u> 4 weeks 0 in both arms <u>Deaths</u> 4 weeks 0 in both arms <u>EPS</u> 4 weeks 5.1% Quetiapine 6.5% lithium

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E32. Strength of evidence assessment: quetiapine versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Quetiapine vs. haloperidol	Response Remission YMRS CGI Withdrawals	1 RCT (n=199)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine vs. lithium	Response Remission YMRS Withdrawals	2 RCTs (n=456)	See table	High	Inconsistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 7. Risperidone for Acute Mania

Appendix Table E33. Characteristics of eligible studies: Risperidone for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Smulevich, 2005 ¹⁵ RCT Multisite 2 Continents Industry RoB Moderate 15572276	N = 438 Mean Age 40 Female 47% White 65% BP-I 100% Inpatient	Mania; YMRS ≥ 20 and MADRS ≤ 20 First Manic Episode Schizoaffective Substance Abuse Other Mental Health Taking Other Meds	Risperidone 1-6 mg/day (mean 4.2 mg/day)	C1: Placebo C2: Haloperidol 2-12 mg/day (mean 8.0 mg/day)	12 weeks (12 week outcomes excluded due to attrition)	BPRS CGI-S GAS MADRS YMRS Withdrawal 48% at 12 weeks 12% at 3 weeks
Khanna, 2005 ⁴⁰ RCT Multisite India Industry RoB Moderate 16135859	N = 290 Mean Age 35 Female 38% Race NR BP-I 100% Inpatient	Mania; YMRS ≥ 20 Schizoaffective Substance Abuse Other Mental Health Taking Other Meds	Risperidone 1-6 mg/day	Placebo	3 weeks	CGI-S MADRS PANSS YMRS Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Segal, 1998 RCT Singlesite South Africa Industry/University RoB Moderate 9617509	N = 45 Mean Age 34 Female 78% Race NR BP-I 100% Inpatient	Mania; DSM-IV criteria for Bipolar Manic Phase Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Risperidone 6 mg/day	C1: Placebo C2: Haloperidol 10 mg/day C3: Lithium 0.6-1.2 mmol/L	4 weeks	BPRS CGI Unknown Scale - Not reported whether global improvement or severity scale is being reported GAF MRS Seclusion - Hours of eclusion - Proportion of patients needing SAS Withdrawal NR

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table E34. Summary risk of bias assessments: risperidone for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Risperidone	Smulevich, 2005 ¹⁵ Industry 15572276	Moderate	Randomization and blinding procedures not well-described. Some participants treated in open-label fashion. 12% dropout.
	Khanna, 2005 ⁴⁰ Industry 16135859	Moderate	Randomization and blinding procedures not described. Handling of data from missing persons not described. 20% dropout.
	Segal, 1998 ⁴¹ Industry/University 9617509	Moderate	Randomization not described, patients assigned consecutively which infers both a lack of randomization and a likelihood of a lack of allocation concealment.

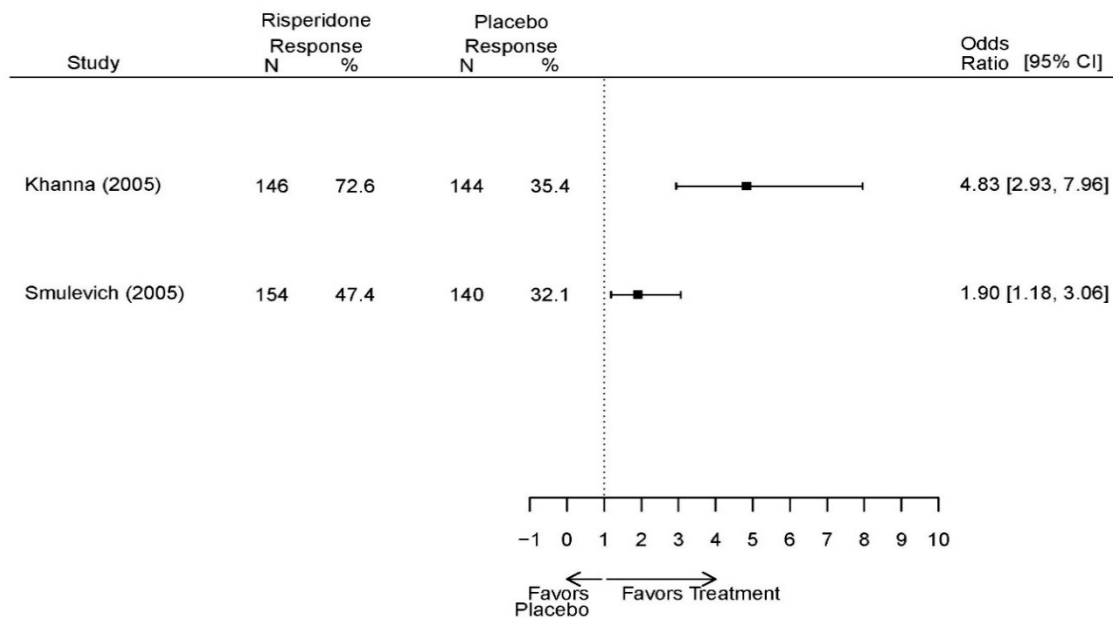
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Risperidone Forest Plots

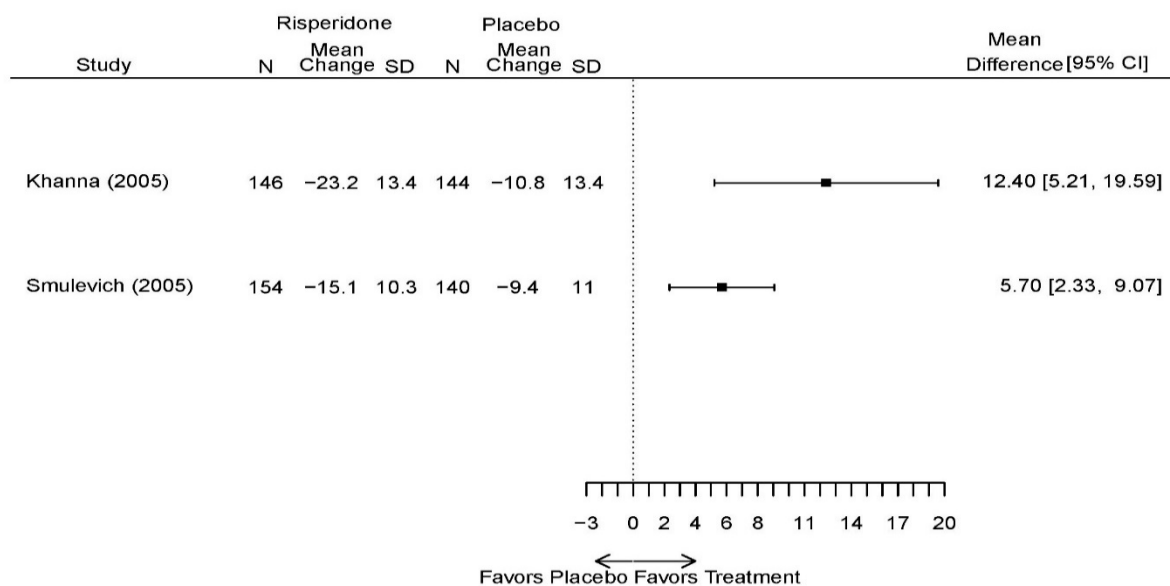
Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

Appendix Figure E69. Risperidone vs. placebo – response

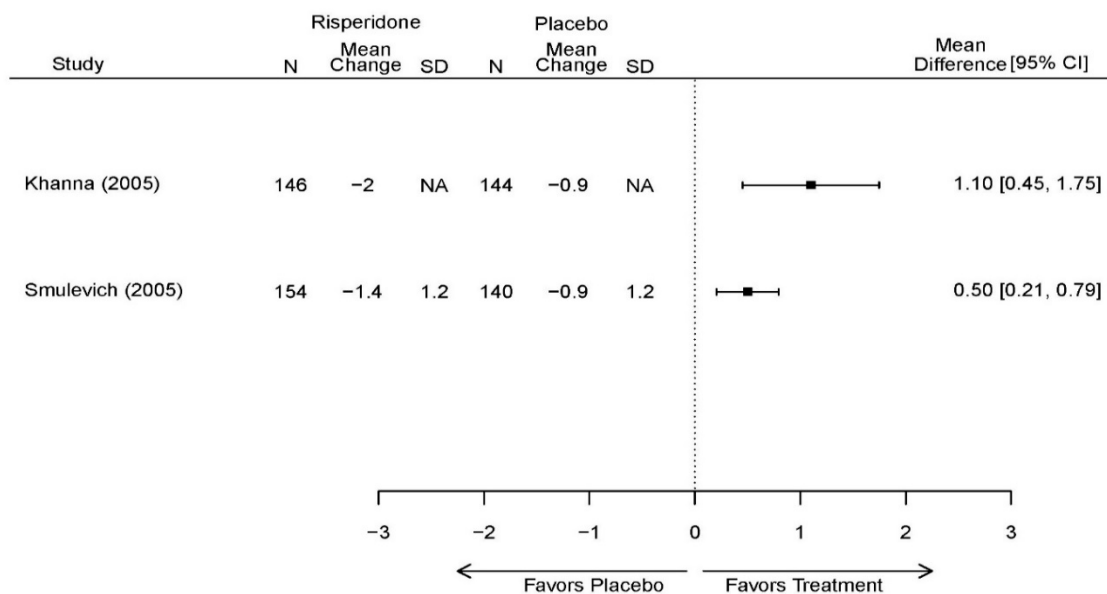
Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



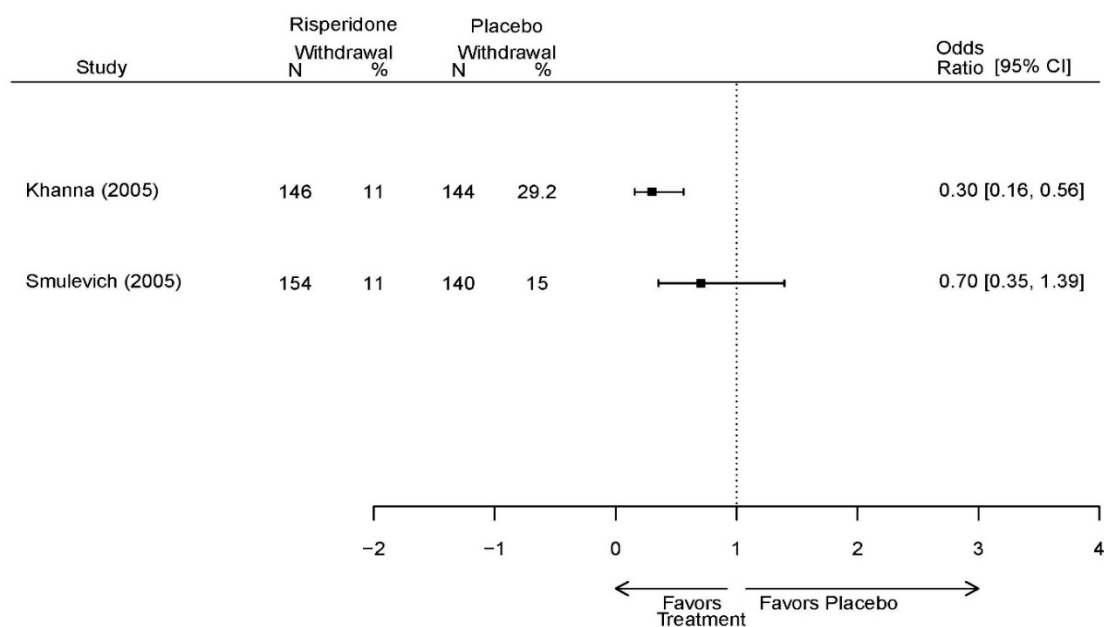
Appendix Figure E70. Risperidone vs. placebo – YMRS
Difference in Mean Change in YMRS from Baseline to Last Measurement



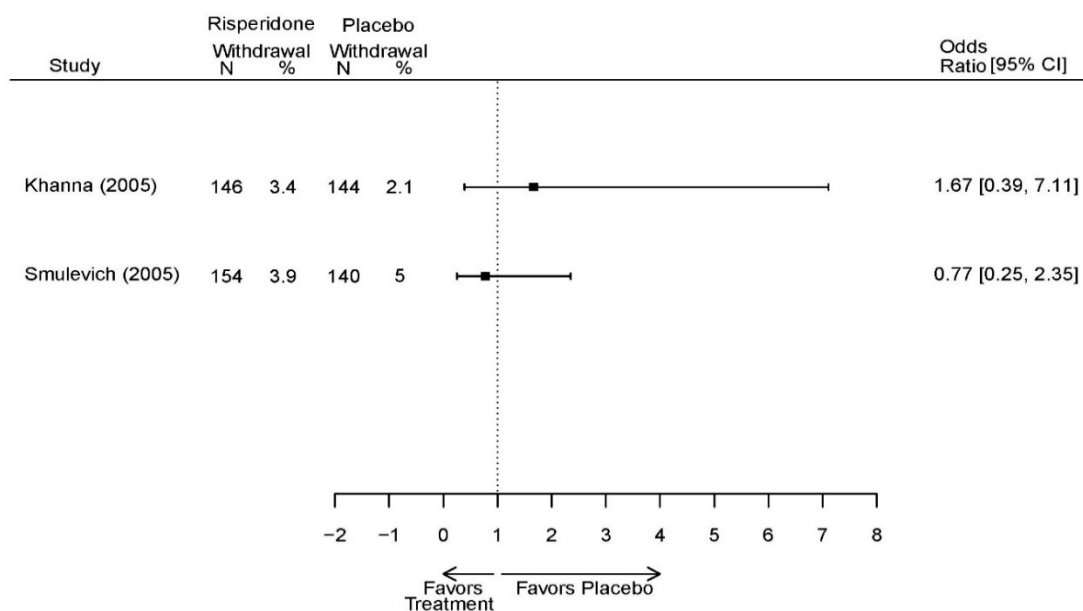
Appendix Figure E71. Risperidone vs. placebo – CGI
Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to Last Measurement



Appendix Figure E72. Risperidone vs. placebo – overall withdrawal
Odds Ratio of Overall Withdrawal



Appendix Figure E73. Risperidone vs. placebo – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Table E35. Outcomes summary: risperidone versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Risperidone	Khanna, 2005 ⁴⁰ 16135859 Moderate	See forest plot E69 above for Response	See forest plot E70 above for YMRS MADRS 3 weeks Mean change Risperidone: -3.2 (0.4) Placebo: -2.5, (0.34) P<0.001)	See forest plot E70 above for CGI	See forest plot E72, E73 above for Withdrawal	<u>Serious Adverse Events</u> 3 weeks 0 in both arms <u>Deaths</u> 3 weeks 0 in both arms <u>EPS</u> 3 weeks 6.0% placebo 36.0% Risperidone
	Smulevich, 2005 ¹⁵ 15572276 Moderate	See forest plot E69 above for Response	See forest plot E70 above for YMRS	See forest plot E70 above for CGI <u>GAS</u> 3 week Risperidone - 17.1(1.8) Placebo -10.3(1.7) No Statistical Tests reported	See forest plot E72, E73 above for Withdrawal	<u>No reported SAE</u> <u>EPS</u> Mean ESRS score increases greater for haloperidol than risperidone (p<0.001)

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E36. Strength of evidence assessment: risperidone versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Risperidone vs. placebo	Response 3 wks YMRS 3 wks CGI 3 wks	2 RCTs (n=584)	Favors Risperidone	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E37. Outcomes summary: risperidone versus active comparator for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Risperidone vs. haloperidol	Smulevich, 2005 ¹⁵ 15572276 Moderate	<u>Response</u> 3 weeks Risperidone 48% Haloperidol 47% NS	<u>YMRS Change</u> 3 week Risperidone - 15.1(10.3) Haloperidol - 13.9(10.3) NS	<u>CGI-S Change</u> 3 week Risperidone -1.4(1.2) Haloperidol -1.3(1.1) NS <u>GAS</u> 3 week Risperidone - 17.1(1.8) Haloperidol - 13.9(10.3) NS	<u>Withdrawal lack of efficacy</u> Risperidone 4% Haloperidol 3% <u>Withdrawal adverse events</u> Risperidone 3% Haloperidol 1%	<u>Serious Adverse Events</u> 12 weeks 0 in both arms <u>Deaths</u> 12 weeks 0 in both arms <u>EPS</u> NR

Drub	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
	Segal, 1998 ⁴¹ 9617509 Moderate	<u>NR</u>	<u>MRS</u> 4 weeks NS	<u>CGI</u> 4 weeks NS <u>GAF</u> 4 weeks NS	NR	<u>Serious Adverse Events</u> 4 weeks 0 in both arms <u>Deaths</u> 4 weeks 0 in both arms <u>EPS</u> NR

Abbreviations: AE=Adverse Events; CI=Confidence Interval; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions; Severity Scale; EPS=extrapyramidal symptoms; GAF=Global Assessment of Functioning Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Syndrome Scale; MRS=Mania Rating Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RoB=Risk of Bias; SD=Standard Deviation; SE=standard error; YMRS = Young Mania Rating Scale

Appendix Table E38. Strength of evidence assessment: risperidone versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Risperidone vs. haloperidol	Response 3 wks YMRS 3 wks CGI-S 3 wks	2 RCTs (n=438)	See table above	Moderate	Consistent	Direct	Imprecise	Insufficient
Risperidone vs. lithium	YMRS 4 wks CGI 4 wks GAF 4 wks	1 RCT (n=45)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 8. Ziprasidone for Acute Mania

Appendix Table E39. Characteristics of eligible studies: ziprasidone drug treatments for acute mania by year then first author

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP-I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Potkin, 200542 RCT Multisite 2 Continents Industry RoB Low 16012271	N = 206 Mean Age 40 Female 49% White 62% BP-I 100% Inpatient	Mania; Mania Rating Scale (SADS-C interview derived; Spitzer, 1978) ≥ 14 with score ≥ 2 on four items at screening and admission Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Pregnant/Nursing	Ziprasidone 80-160 mg/day (112 mg/day mean)	Placebo	3 weeks	BMI or Weight CGI-I CGI-S GAF HAM-D MADRS MRS PANSS Withdrawal 41%
Keck, 200343 RCT Multisite 2 Continents Industry RoB Moderate 12668364	N = 210 Mean Age 38 Female 46% Race NR BP-I 100% Inpatient	Mania; Mania Rating Scale (SADS-C interview derived; Spitzer, 1978) ≥ 14 with score ≥ 2 on four items at screening and admission Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Ziprasidone 40-80 mg bid (mean ≈ 130 mg/day)	Placebo	3 weeks	MRS CGI-S CGI-I PANSS GAF Adverse Events AIMS Withdrawal 50%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BAS=Behavioral Approach System; BMI=Body Mass Index; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=comparison; CGI= Clinical Global Impressions; CGI-I=Clinical Global Impressions-Improvement; CGI-S =CGI-Severity; CGI-BP=Clinical Global Impressions Scale-Bipolar; CGI-BP-C= Clinical Global Impressions, Bipolar, Change Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; C-SSRS=Columbia Suicide Severity Rating Scale; DAI-10=Drug Attitude Inventory, 10 question version; DIEPSS=Drug-Induced Extra-Pyramidal Symptoms Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; ER=Extended Release; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-A=Hamilton Scale for Anxiety; HAM-D=Hamilton Scale for Depression; HRQL=Health-related quality of life; HRQOL=Health-related quality of life; I=intervention; IDS=Inventory for Depressive Symptoms; LIFE= Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; MRS=Mania Rating Scale; MSRS=Manic state rating scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PRS=Polygenic Risk Scores; PGWB=Psychological General Well-Being Index; PMID=PubMed Identification Number; PRS=Polygenic Risk Scores; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; ROB=risk of bias; SADS-C= Schedule for Affective Disorders and Schizophrenia-Change version; SAE=Serious Adverse Events; SAS=Simpson Angus Scale; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; SLICE=Streamlined Longitudinal Interview Clinical Evaluation; T=Trials; YMRS = Young Mania Rating Scale

Appendix Table E40. Summary risk of bias assessments: ziprasidone for acute mania by year then first author

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Ziprasidone	Keck, 2003 ⁴³ Industry 12668364	Moderate	All core sources of bias appear to have been addressed, however, almost 50% dropout.
	Potkin, 2005 ⁴² Industry 16012271	Low	No sources of bias identified. Well disclosed and reported study.

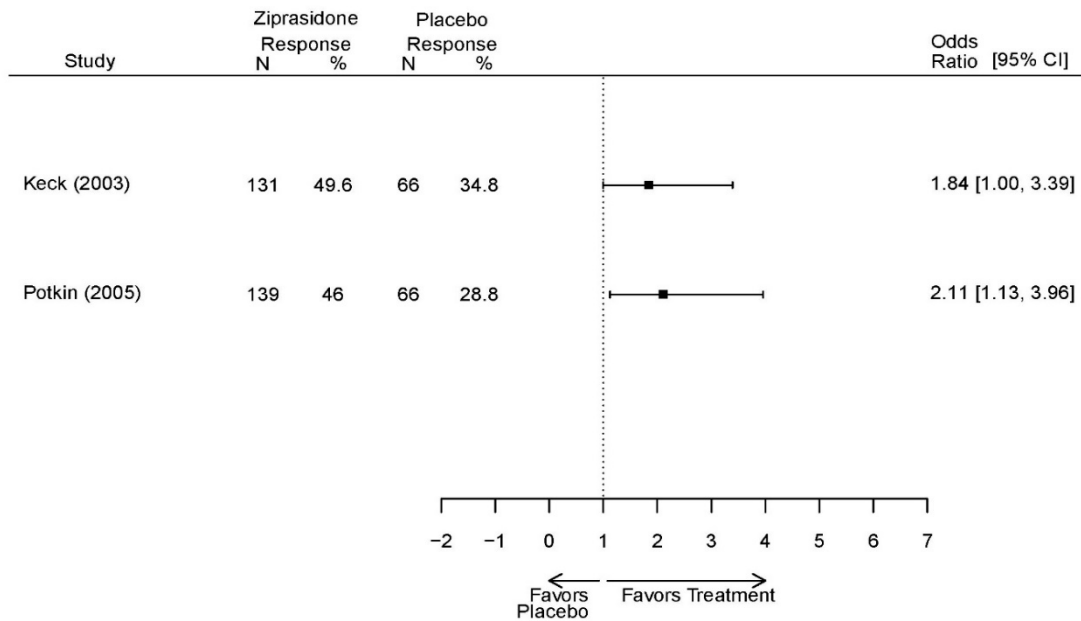
Abbreviations: ITT=Intention to Treat; PMID=PubMed Identification Number; LOCF=last observation carried forward

Ziprasidone Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

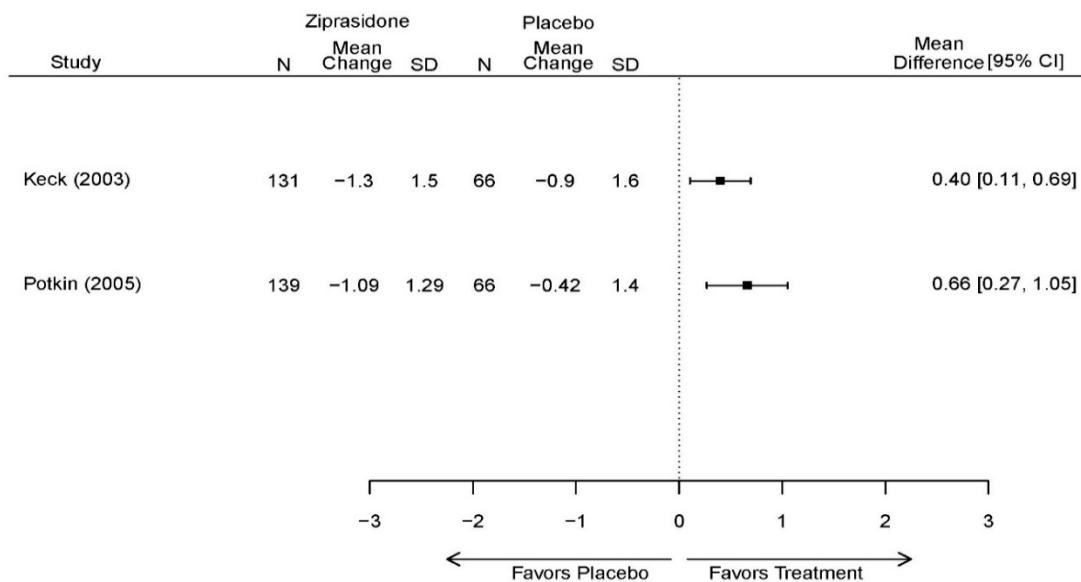
Appendix Figure E74. Ziprasidone vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks

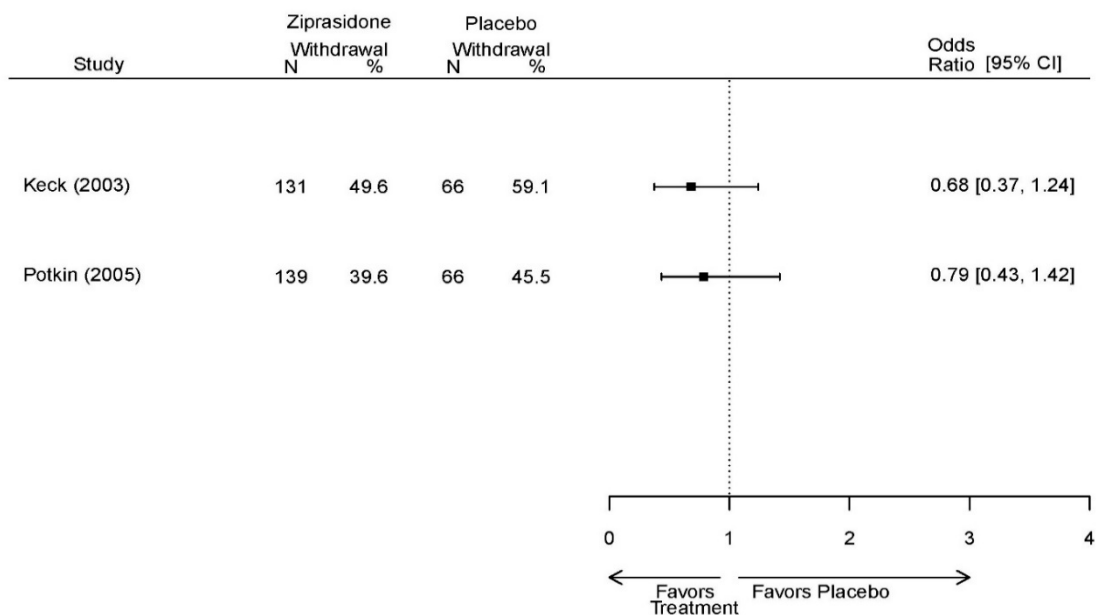


Appendix Figure E75. Ziprasidone vs. placebo – CGI

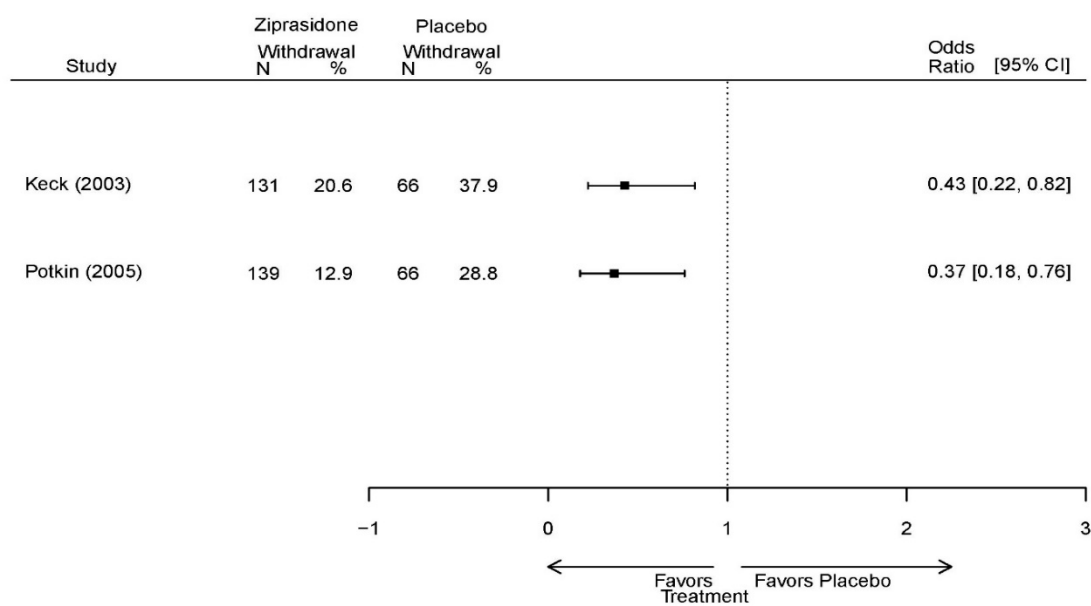
**Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to Last Measurement**



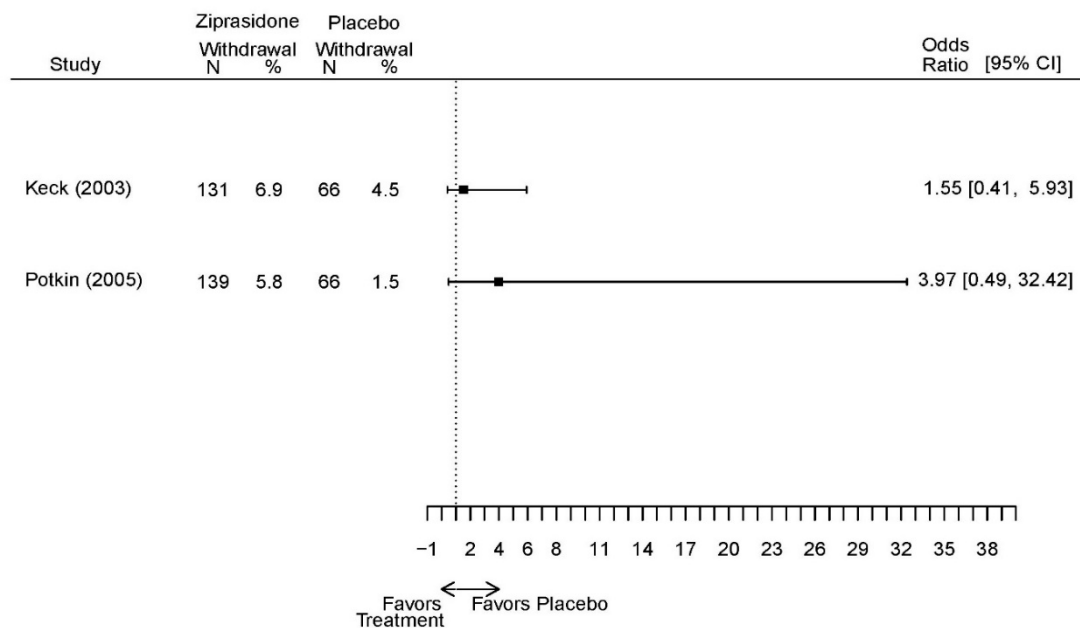
Appendix Figure E76 Ziprasidone vs. placebo – overall withdrawal Odds Ratio of Overall Withdrawal



Appendix Figure E77. Ziprasidone vs. placebo – withdrawal – lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E78. Ziprasidone vs. placebo – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Table E41. Outcomes summary: ziprasidone versus placebo for acute mania

Drug	Study PMID RoB	Responder/Remitter	Symptom	Function	Other	AE
Ziprasidone	Keck, 2003 ⁴³ 12668364 Moderate	See forest plot E74 above for Response	See forest plot above	See forest plot E75 above for CGI GAF 3 weeks F=10.35, df=1, 156, p<0.005 Favors intervention	See forest plots 76, 77, and 78 above	<u>Serious Adverse Events</u> 3 weeks 0 in both arms <u>Deaths</u> 3 weeks 0 in both arms <u>EPS</u> NR
	Potkin, 2005 ⁴² 16012271 Moderate	See forest plot E74 above for Response	See forest plot above	See forest plot E75 above for CGI GAF 3 weeks Favors intervention p ≤.001 No statistical test reported	See plots 76, 77, and 78 above	<u>Serious Adverse Events</u> 3 weeks 1 Ziprasidone <u>Deaths</u> 3 weeks 1 Ziprasidone – Suicide <u>EPS</u> 3 weeks 1.5% placebo 10.8% Ziprasidone

Abbreviations: AE=Adverse Events; ANCOVA=Analysis of Covariance; CGI=Clinical Global Impressions Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAS=Global Assessment Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=Not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; ROB=Risk of Bias; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table E42. Strength of evidence assessment: ziprasidone versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Ziprasidone vs. placebo	Response 3 wks YMRS 3 wks CGI 3 wks	2 RCTs (n=402)	Favors Ziprasidone	Moderate	Consistent	Direct	Imprecise	Low

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 9. Aripiprazole Plus Mood Stabilizer

Appendix Table E43. Characteristics of eligible studies: aripiprazole plus mood stabilizer drug treatments for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
NCT00665366 2013 Unpublished RCT Multiste 3 Continents Industry RoB NA	N = 370 Mean Age 45 Female 54% White 95% BP I 100% Setting NR	Mania, manic or mixed episode, with or without psychotic features Schizoaffective Substance Abuse Other Mental Health Neurological disorders Pregnant/Nursing Labs/Other Conditions	Aripiprazole 5-15 mg/day Adjunctive to valproate or lithium	Placebo Adjunctive to valproate or lithium	12 weeks	Response (≥50% YMRS decrease) Remission (YMRS ≤ 12) YMRS CGI-BP FAST LIFE-RIFT PGI-I Weight change Withdrawal 32%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Jeong, 2012 ⁴⁴ RCT Multisite South Korea Industry 22592508 RoB Low	N = 42 Mean Age 37 Female 64% Race NR BP I 100% Inpatient	Manic; DSM-IV-TR criteria YMRS ≥20 Schizoaffective Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions	Aripiprazole Flexible dosing Mean 20 mg/day Adjunctive to valproic acid (serum level 50-125 mg/mL)	Haloperidol Flexible dosing Mean 5 mg/day Adjunctive to valproic acid (serum level 50- 125 mg/mL)	8 weeks	Response (≥50% YMRS decrease) Remission (YMRS ≤ 12) YMRS CGI-S Drug-induced Extrapyramidal Symptoms Scale Weight gain Withdrawal 7%
Vieta, 2008 ⁴⁵ RCT Multisite/Not Disclosed Industry RoB Moderate 18381903	N = 384 Mean Age 42 Female 54% White 91% BP I 100% Outpatient	Manic/Mixed episode; Partial responders to Lithium or Valproate; YMRS ≥16 with decrease of ≤25% after 6 weeks of stabilization treatment Substance Abuse Other Mental Health	Aripiprazole 15-30 mg/day (19.0 mg/day) Adjunctive to lithium/ divalproex/valproate	Placebo Adjunctive to lithium/divalproex/ valproate	6 weeks	YMRS Response Adverse Events EPS CGI-BP Withdrawal 19%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S= Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premord Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E44. Summary risk of bias assessments: arirprizaole plus mood stabilizers for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Aripiprazole	Jeong, 2012 ⁴⁴ Industry 22592508	Low	May be underpowered and raters may not be blinded. 7% dropout.
	Vieta 2008 ⁴⁵ Industry 18381903	Moderate	Randomization and blinding procedures not disclosed.

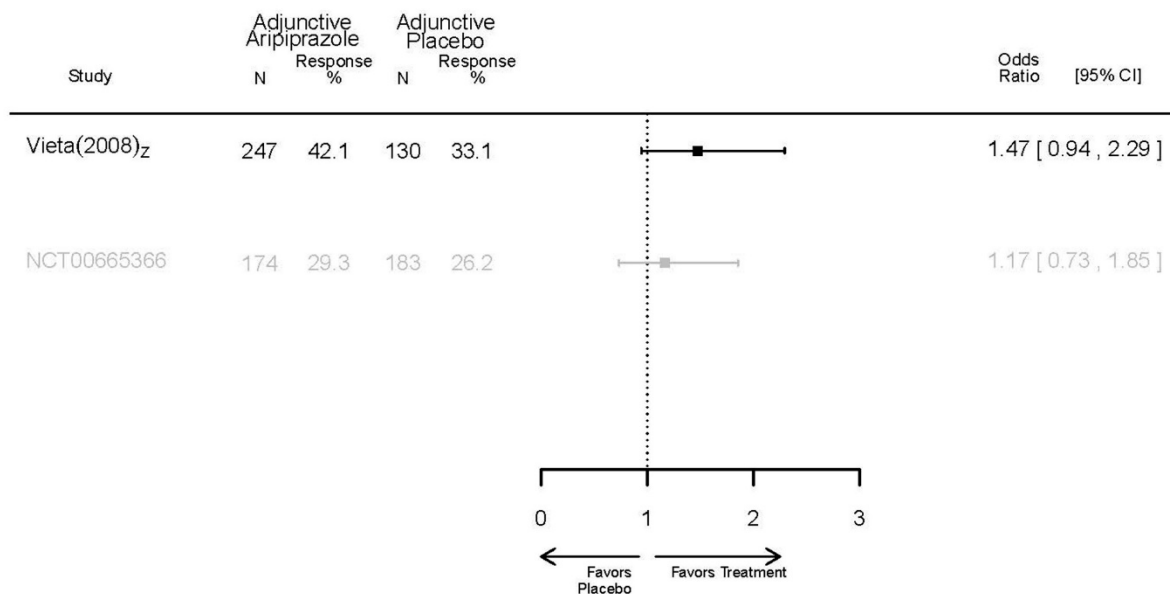
Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Antipsychotics Plus Mood Stabilizer Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

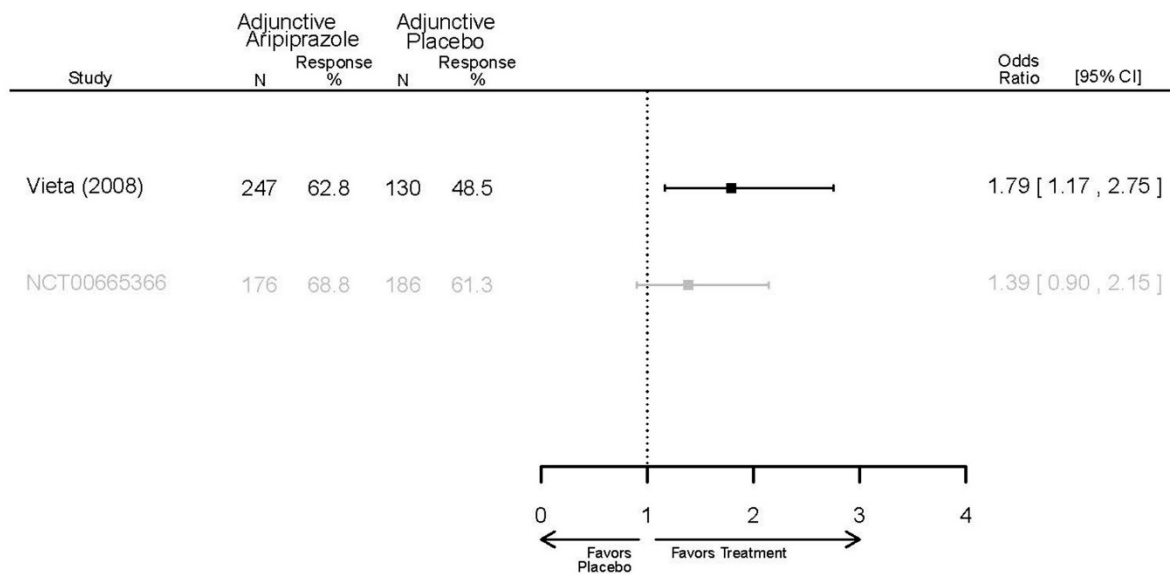
Appendix Figure E79. Adjunctive aripiprazole vs. placebo – 3 week response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



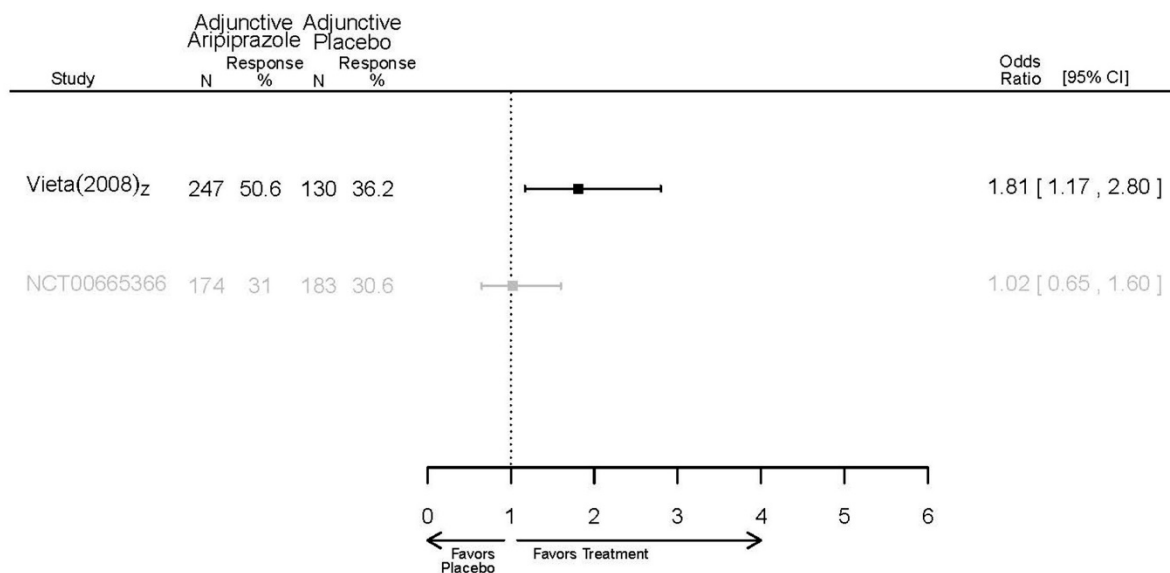
Appendix Figure E80. Adjunctive aripiprazole vs. placebo – last response

Odds Ratio of Response (> 50% Reduction in YMRS) at Last Measurement

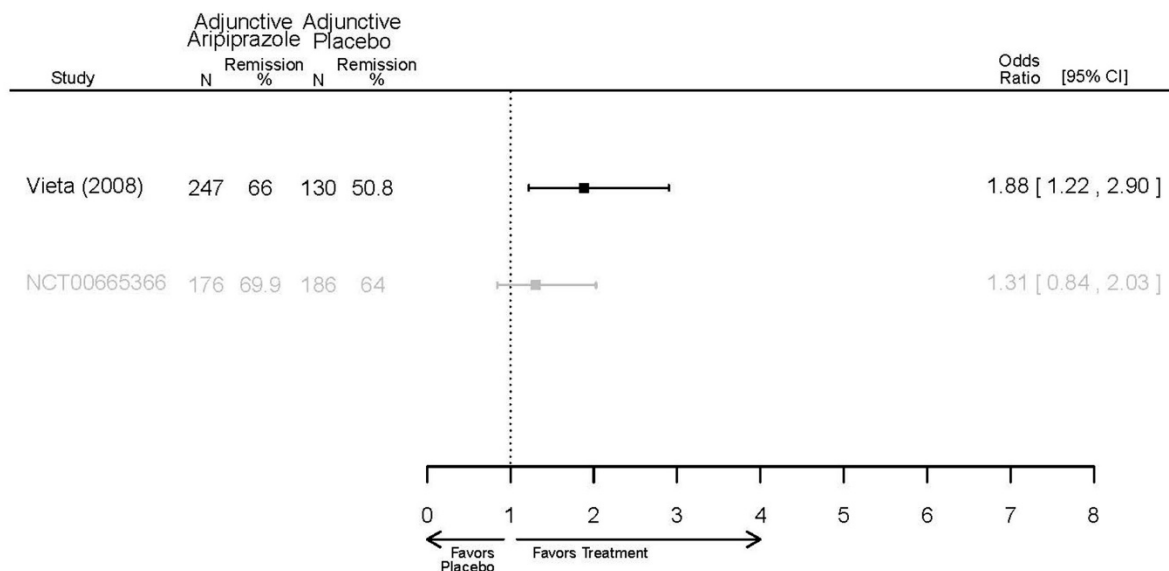


Appendix Figure E81. Adjunctive aripiprazole vs. placebo – 3 week remission

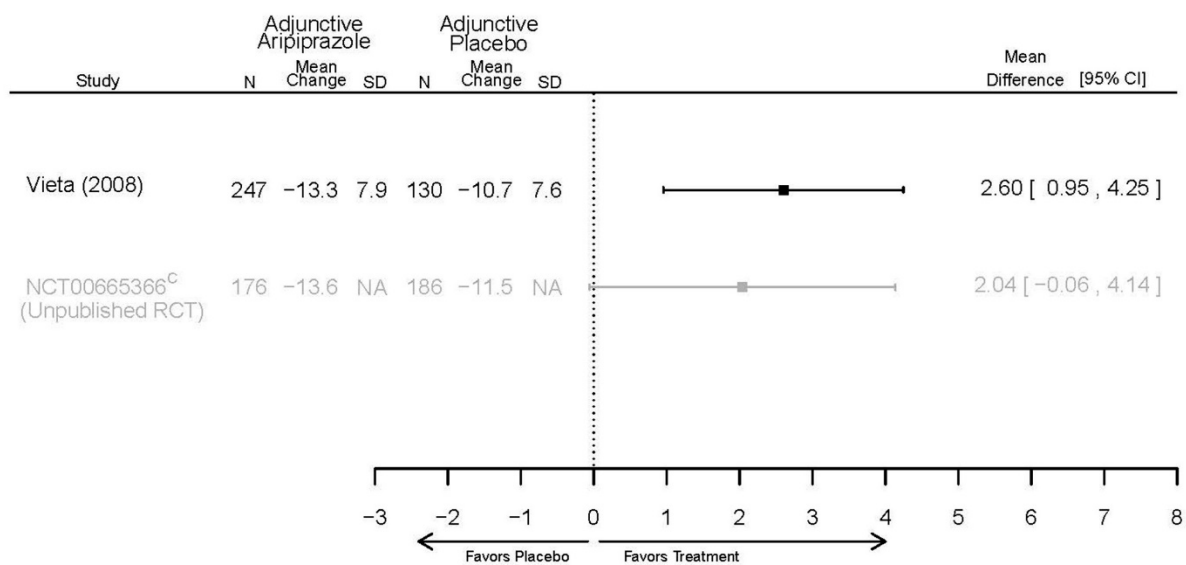
Odds Ratio of Remission (YMRS ≤ 12) at 3 Weeks



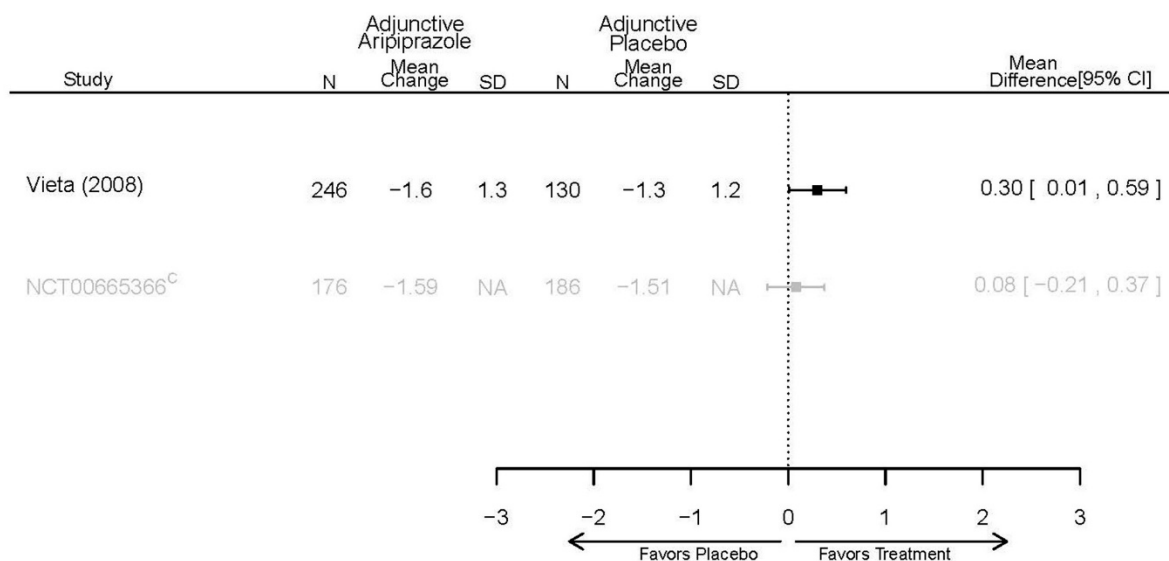
Appendix Figure E82. Adjunctive aripiprazole vs. placebo – last remission
Odds Ratio of Remission (YMRS ≥ 12) at Last Measurement



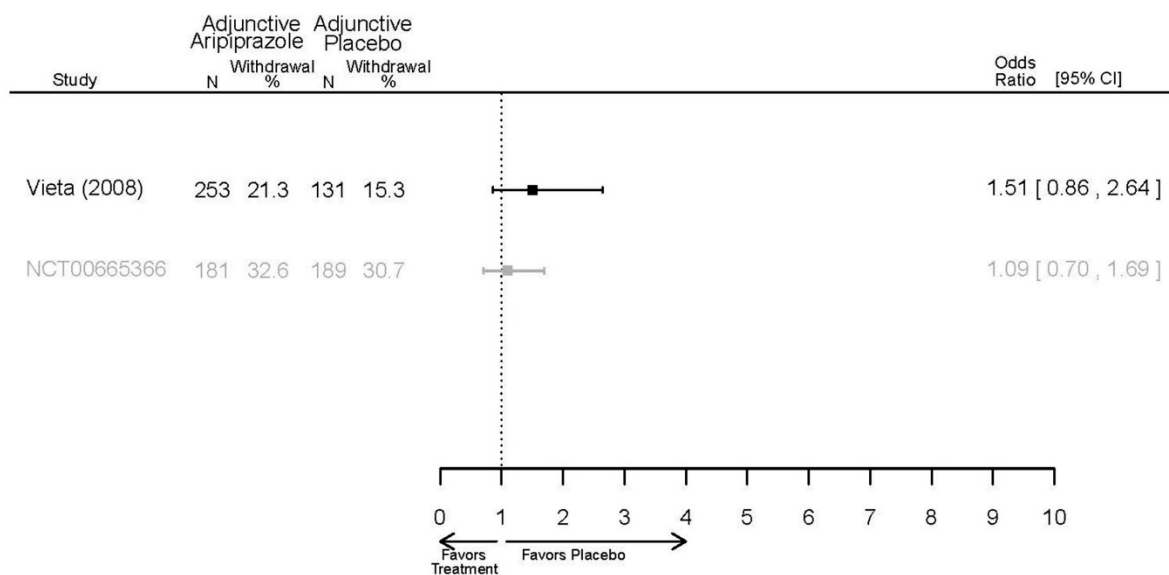
Appendix Figure E83. Adjunctive aripiprazole vs. placebo – YMRS
Difference in Mean Change in YMRS from Baseline to Last Measurement



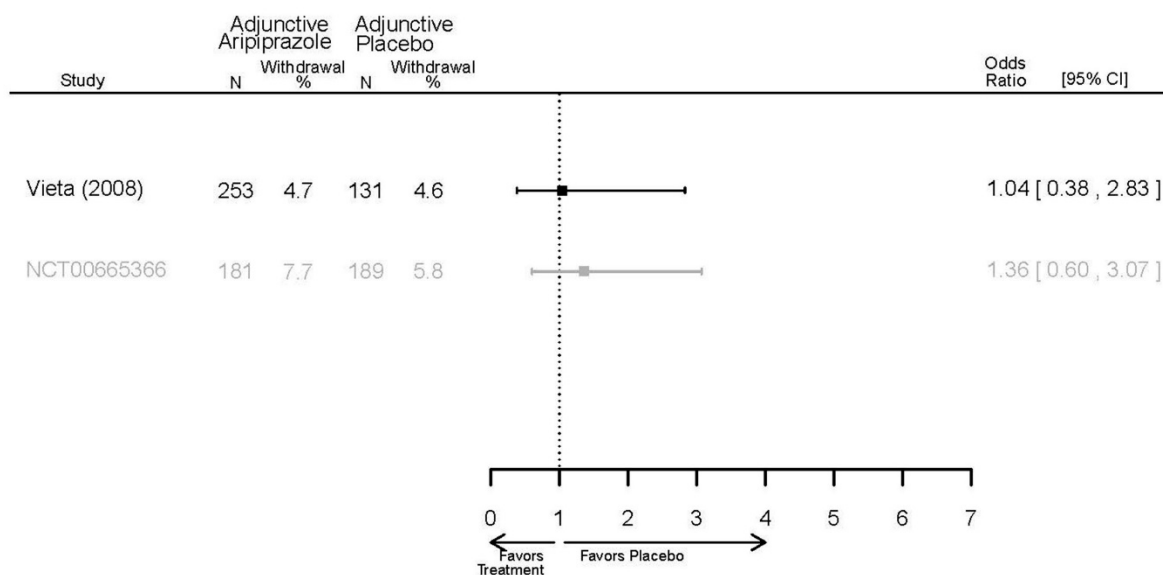
Appendix Figure E84. Adjunctive aripiprazole vs. placebo – CGI
Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to Last Measurement



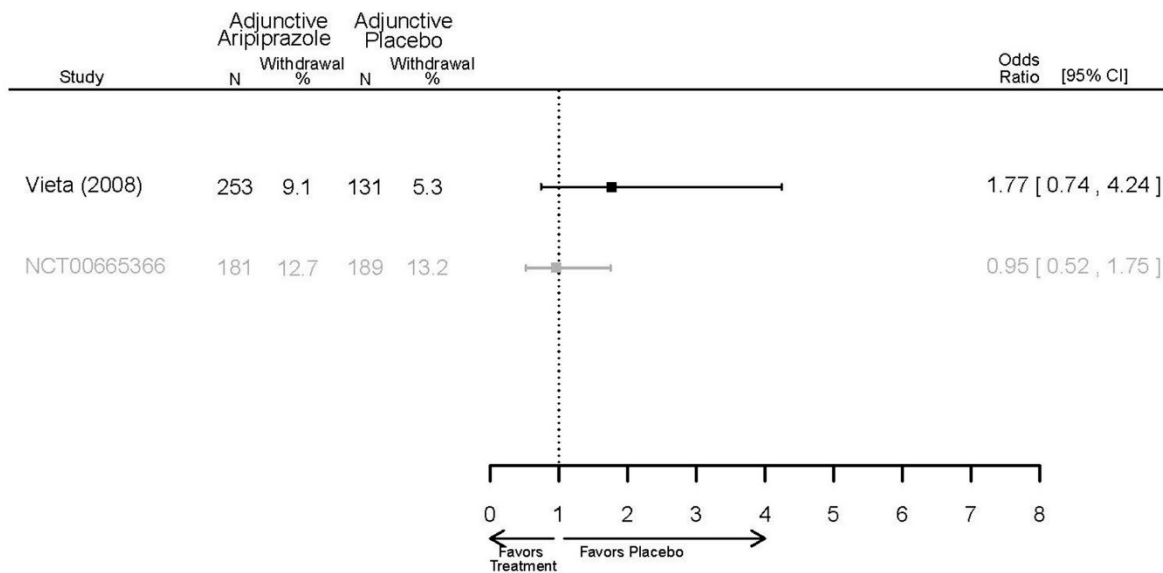
Appendix Figure E85. Adjunctive aripiprazole vs. placebo – overall withdrawal
Odds Ratio of Withdrawal due to All Causes at Last Measurement



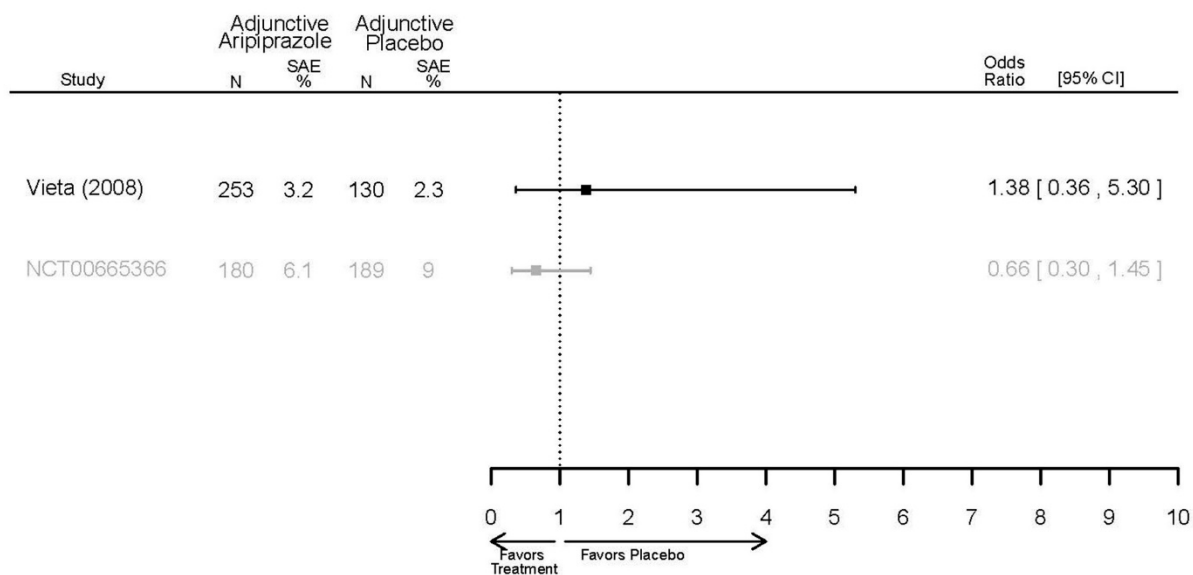
Appendix Figure E86. Adjunctive aripiprazole vs. placebo – withdrawal – lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at Last Measurement



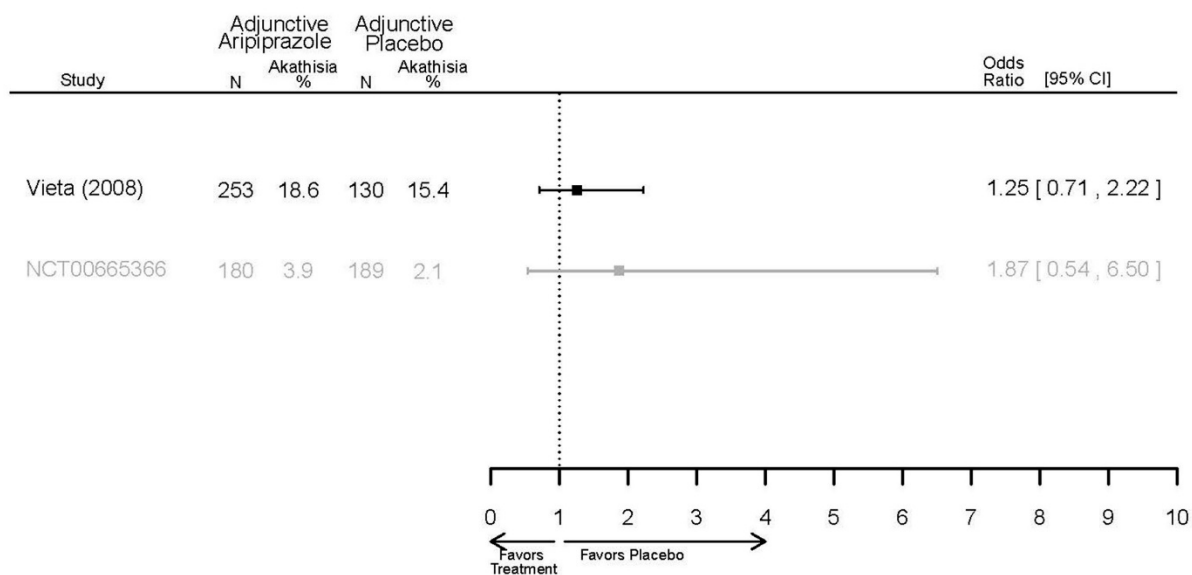
Appendix Figure E87. Adjunctive aripiprazole vs. placebo – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events at Last Measurement



Appendix Figure E88. Adjunctive aripiprazole vs. placebo – serious adverse events
Odds Ratio of Serious Adverse Event at Last Measurement



Appendix Figure E89. Adjunctive aripiprazole vs. placebo – akathisia
Odds Ratio of Akathisia



Appendix Table E45. Outcomes summary: aripiprazole plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Aripiprazole adjunctive vs. placebo	NCT00665366 2013	See forest plots E79, E80, E81, and E82 above.	See forest plot E83 above.	See forest plot E84 above for CGI	See forest plot E85, E86 and E87 above for Withdrawals.	<p>See forest plot E88, E89, and E90 above for adverse events.</p> <p><u>Very Serious AE</u> 1 reported case of suicide ideation related to depression in the aripiprazole arm</p> <p>1 case of acute respiratory failure in the Aripiprazole arm</p> <p><u>Cases of Severe Depression</u> 12 weeks NS Aripiprazole = 4/180 Placebo= 2/189 OR = 2.05 (0.37, 16.72) ; P = 0.38</p> <p><u>Cases of Manic Reaction or Relapse</u> 12 weeks NS Aripiprazole = 2/180 Placebo= 7/189 OR = 0.31 (0.04, 1.34) ; P = 0.18</p>

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
	Vieta, 2008 ⁴⁵ 18381903 Moderate	See forest plots E79, E80, E81, and E82 above.	See forest plot E83 above.	NR	See forest plot E85, E86 and E87 above for Withdrawals.	See forest plot above. <u>EPS</u> 6 weeks Favors Placebo Aripiprazole =71/253 Placebo=18/130 OR = 2.41 (1.39, 4.37) ; P = 0.002 <u>Normalized Weight Change</u> (> 7% change) 6 weeks NS Aripiprazole = 7/253 Placebo= 5/130 OR = 0.71 (0.22, 2.50) ; P = 0.57 <u>Cases of Psychiatric</u> <u>Disorder</u> 6 weeks NS Aripiprazole = 6/253 Placebo= 3/130 OR = 1.00 (0.25, 5.11) ; P = 0.97

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E46. Strength of evidence assessment: aripiprazole plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Aripiprazole adjunctive vs. placebo	Response 6 wks Remission 6 wks YMRS 6 wks CGI-BP 6 wks Withdrawals	2 RCTs (n=752)	See forest plots	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E47. Outcomes summary: aripiprazole plus mood stabilizers versus active comparison for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Aripiprazole adjunctive vs. haloperidol adjunctive	Jeong, 2012 ⁴⁴ 22592508 RoB	<u>Response</u> 3 weeks NS Aripiprazole= 20 (71.4%) Haloperidol= 11 (78.6%) No statistical test reported 8 weeks NS Aripiprazole=24 (85.7%) Haloperidol= 13 (92.9%) No statistical test reported <u>Remission</u> 3 weeks NS Aripiprazole= 18 (64.3%) Haloperidol= 9 (64.3%) No statistical test reported 8 weeks NS Aripiprazole= 23 (82.1%) Haloperidol= 12 (85.7%) No statistical test reported	<u>Change in YMRS</u> 8 weeks NS Change (SE) Aripiprazole= -16.3 (1.6) Haloperidol= -17.5 (2.3) P=0.66	<u>Change in CGI-BP</u> 8 weeks NS Change (SE) Aripiprazole= 2.0 (0.2) Haloperidol= 1.7 (0.3) P=0.41	<u>Overall Withdrawal</u> 8 weeks NS Aripiprazole = 2 (7.1%) Haloperidol = 1 (7.1%) No statistical test reported <u>Withdrawal due to Lack of Efficacy</u> 8 weeks NS Aripiprazole =1 (3.6%) Haloperidol =0 (0%) No statistical test reported <u>Withdrawal due to AEs</u> 8 weeks NS Aripiprazole = 1 (3.6%) Haloperidol = 1 (7.1%) No statistical test reported	<u>Extrapyramidal Symptoms</u> 8 weeks Favors Aripiprazole Aripiprazole =32.1% Haloperidol =50% No statistical test reported <u>Normalized Weight Change (>7% change)</u> 8 weeks Favors Comparator Aripiprazole =18/28 Haloperidol =4/14 P=0.049 <u>Emergent Mood Episode (Depression)</u> 8 weeks Aripiprazole =2/28 Haloperidol =3/14 No statistical test reported <u>Akathisia</u> 8 weeks Aripiprazole =7/28 Haloperidol =2/14 No statistical test reported

Abbreviations: AE=Adverse Events; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S-Clinical Global Impressions, Bipolar, Severity Scale; HAMD=Hamilton Scale for Depression; NS=not significant; PMID=PubMed Identification Number; ROB=risk of bias; SAE; Serious Adverse Events; SE=standard error; YMRS = Young Mania Rating Scale

Appendix Table E48. Strength of evidence assessment: aripiprazole plus mood stabilizers versus active comparison for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Aripiprazole adjunctive vs. haloperidol adjunctive	3 weeks Response Remission YMRS CGI-BP Withdrawal – overall Withdrawal – lack of efficacy Withdrawal – Aes	1 RCT (n=42)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 10. Asenapine Plus Mood Stabilizer

Appendix Table E49. Characteristics of eligible studies: asenapine plus mood stabilizer drug treatments for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Szegedi, 2012 ⁴⁶ RCT Multisite 4 Continents Industry RoB Moderate 22198448	N = 324 Mean Age 39 Female 43% White 57% BP I 100% Outpatient	Mania; YMRS ≥ 20 Current episode ≤3 months Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions First Manic Episode	Asenapine 5-10 mg BID (Mean 11.8 mg/day) Adjunctive to Lithium 0.6-1.2 mmol/L (mean 12.8 mg/day) OR Valproate 50-125 mcg/mL (mean 11.0 mg/day)	Placebo Adjunctive to Lithium 0.6-1.2 mmol/L (mean 12.8 mg/day) OR Valproate 50-125 mcg/mL (mean 11.0 mg/day)	3 weeks (12 week >50% attrition)	YMRS MADRS CGI-BP ISST SF-36 RDQ Adverse Events Withdrawal 37%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S= Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premordid Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E50. Summary risk of bias assessments: asenapine plus mood stabilizers for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Asenapine	Szegedi, 2012 ⁴⁶ Industry 22198448	Moderate (3 week outcomes)	Statistically significant difference in the number of patients who complete the trial for both arms, but 'if patients who had recurrence were also counted as completers, then completion rates were 73.3% for olanzapine and 67.3% for lithium' -- which are similar but dropout rates are still moderately high (30%).

Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Appendix Table E51. Outcomes summary: asenapine plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Asenapine adjunctive vs. placebo	Szegedi, 2012 ⁴⁶ 22198448 Moderate	<u>Response</u> No difference between groups OR 1.14 (0.71, 1.84) <u>Remission</u> No difference between groups OR 1.47 90.90, 2.42)	<u>YRMS</u> Favors asenapine Mean difference 2.03 (0.26, 3.80)	<u>CGI-BP-S</u> Favors asenapine Mean difference 0.30 (0.08, 0.52)	NR at 3 weeks	Serious Adverse Events 52 weeks 1 Asenapine Deaths 52 weeks 1 Asenapine – suicide EPS 52 weeks 12% placebo 9.5% Asenapine

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E52. Strength of evidence assessment: asenapine plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Asenapine adjunctive vs. placebo	Response 3 wks YMRS 3 wks CGI-BP 3 wks	1 RCT (n=324)	NS	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 11. Olanzapine Plus Mood Stabilizer

Appendix Table E53. Characteristics of eligible studies: olanzapine plus mood stabilizer drug treatments for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Conus, 2015 ⁴⁷ RCT Single-site Australia Industry RoB Low 26485297	N = 83 Mean Age 22 Female 32% Race NR BP I 100% Inpatient	First manic or mixed episode; YMRS ≥ 20 Other Mental Health Neurological Disorders Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Olanzapine 5 mg/day adjusted by 2.5 mg/day Adjunctive to lithium 500 mg/day increased by 500 mg/twice daily	Chlorpromazine 100 mg/day adjusted by 50- 100 mg/day Adjunctive to lithium 500 mg/day increased by 500 mg/twice daily	8 weeks	Response ($\geq 50\%$ YMRS reduction) Remission (YMRS \leq 12) Symptomatic recovery (YMRS ≤ 12 and HAMD-21 < 7) Efficacy YMRS CGI-BP BPRS HAMD-21 SAPS SANS ASI PAS GAF QLS Adverse events UKU Withdrawal 14%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Xu, 2015 ¹⁹ RCT Single-site China Government RoB Low 26060401	N = 120 Mean Age 31 Female 52% Race NR BP I 100% Setting NR	First manic; YMRS ≥ 17 Substance Abuse Neurological Disorders Taking Other Meds Pregnant/Nursing	Olanzapine 10 mg/day + Valproate 600 mg/day	C1: Olanzapine 10 mg/day Flexible dosing 5-20 mg/day C2: Valproate 600 mg/day alone	4 weeks	Efficacy YMRS CGI-BP Adverse events Extrapyramidal symptoms SAS Withdrawal 5%
Houston, 2009 ⁴⁸ RCT US and Puerto Rico Industry RoB High 19778495	N = 202 Mean Age 39 Female 59% White 51% BP I 100% Outpatient	Mixed Episode; YMRS ≥ 16 HDRS-21 (inadequate response to divalproex) First Manic Episode Taking Other Meds Labs/Other Conditions	Olanzapine 5-20 mg/day Adjunctive to divalproex (adjusted for blood levels between 75- 125 $\mu\text{g/mL}$)	Divalproex alone (adjusted for blood levels between 75- 125 $\mu\text{g/mL}$)	6 weeks	Response ($\geq 50\%$ decrease HDRS-21 and $\geq 25\%$ decrease YMRS) Remission (YMRS ≤ 12 and HDRS-21 ≤ 8) Efficacy HDRS-21 YMRS CGI-BP Adverse events Extrapyramidal symptoms Withdrawal 42%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2008a ⁴⁹ RCT Multisite 3 Continents Industry RoB Moderate 18245032	N = 118 Mean Age 41 Female 58% Race NR BP I 100% Inpatient and Outpatient	Manic or Mixed Episode; YMRS ≥20 Labs/Other Conditions	Olanzapine 10-30 mg/day Adjunctive to carbamazepine 400-1200 mg/day	Placebo Adjunctive to carbamazepine 400-1200 mg/day	6 weeks blinded (26 weeks open- label extension)	Efficacy YMRS CGI (multiple subscales) MADRS Adverse events Extrapyramidal symptoms SAS BAS AIMS Withdrawal 28% at 6 weeks
Tohen, 2002a ⁵⁰ RCT Multisite US and Canada Industry RoB High 11779284 15337326 ⁵¹ 15572737 ⁵²	N = 344 Mean Age 41 Female 52% White 85% Diagnosis NR Outpatient	Manic or Mixed Episode; YMRS ≥ 16 First Manic Episode Labs/Other Conditions	Olanzapine 10 mg/day with flexible dosing from 5-20 mg/day Adjunctive to ongoing open-label valproate or lithium	Placebo Adjunctive to ongoing open- label valproate or lithium	6 weeks	Efficacy YMRS HAM-D PANSS CGI Remission Adverse Events Extrapyramidal symptom Withdrawal 30%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S== Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premordium Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to

Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E54. Summary risk of bias assessments: olanzapine plus mood stabilizers for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Olanzapine	Conus, 201547 Industry 26485297	Low	Physician and patients may not be blinded. Dropout balanced and accounted for in analysis.
	Xu, 201519 Government 26060401	Low	Well-constructed, described, and reported study. 5% dropout.
	Houston, 200948 Industry 19778495	High	Randomization and blinding procedures not described. 42% dropout.
	Tohen, 2008a49 Industry 18245032	Moderate	Blinding procedure not described. 28% dropout.
	Tohen, 2002a50 Industry 11779284	High	Randomization and blinding procedures not described. 30% dropout.

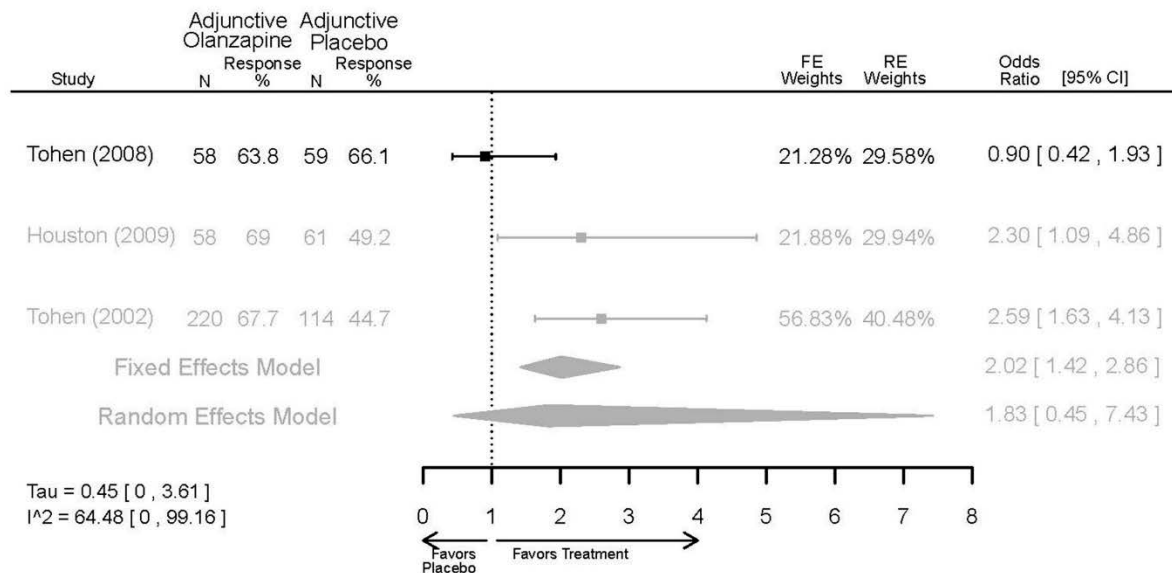
Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Antipsychotics Plus Mood Stabilizer Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

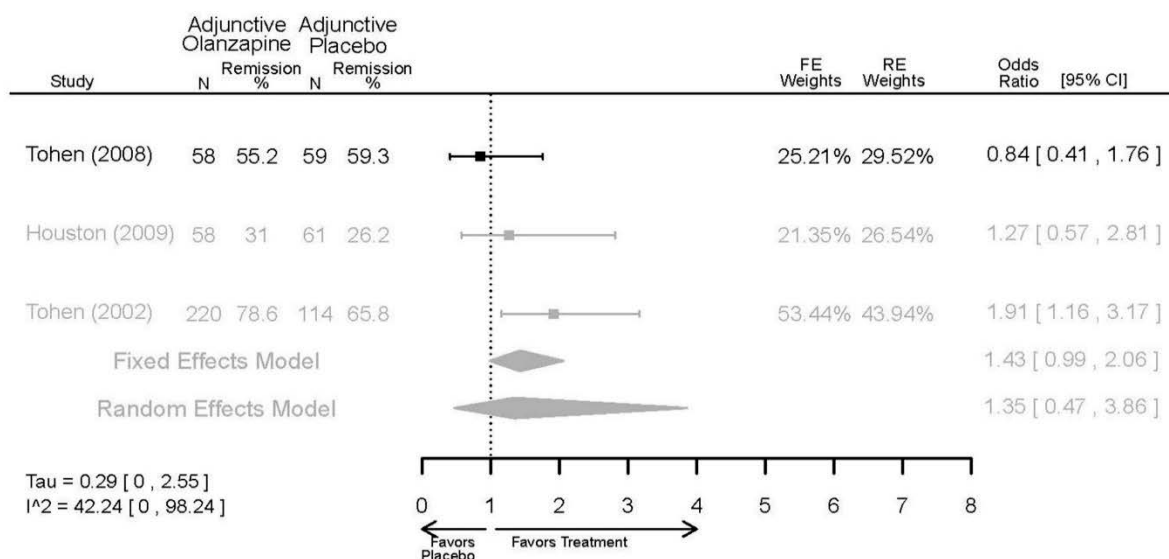
Appendix Figure E90. Adjunctive olanzapine vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at Last Measurement (6 Weeks)



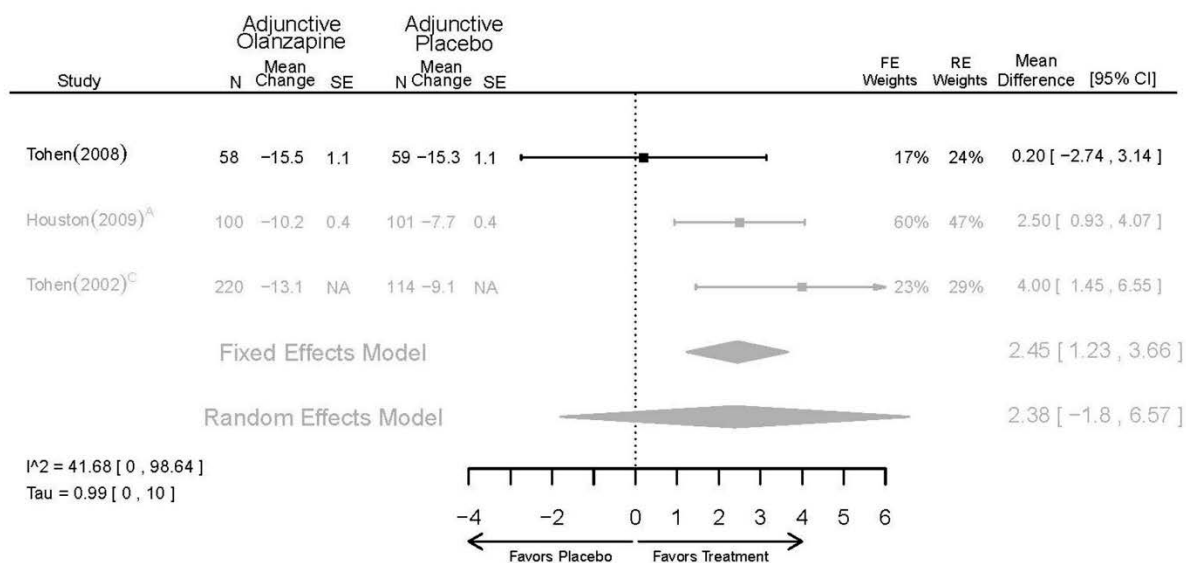
Appendix Figure E91. Adjunctive olanzapine vs. placebo – remission

Odds Ratio of Remission (YMRS = 12) at Last Measurement (6 Weeks)



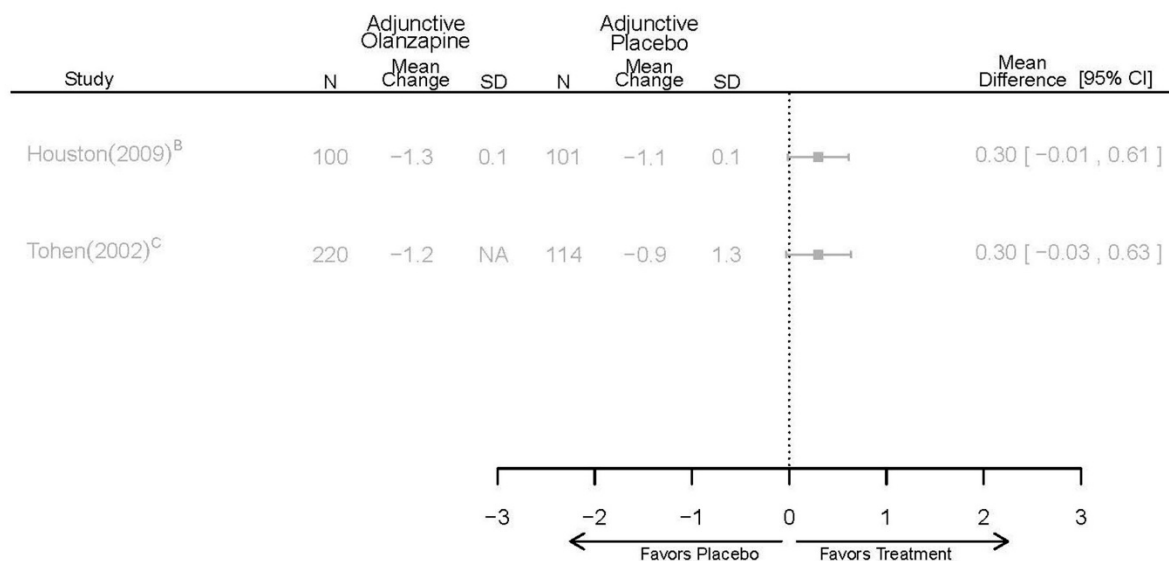
Appendix Figure E92. Adjunctive olanzapine vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to 6 Weeks



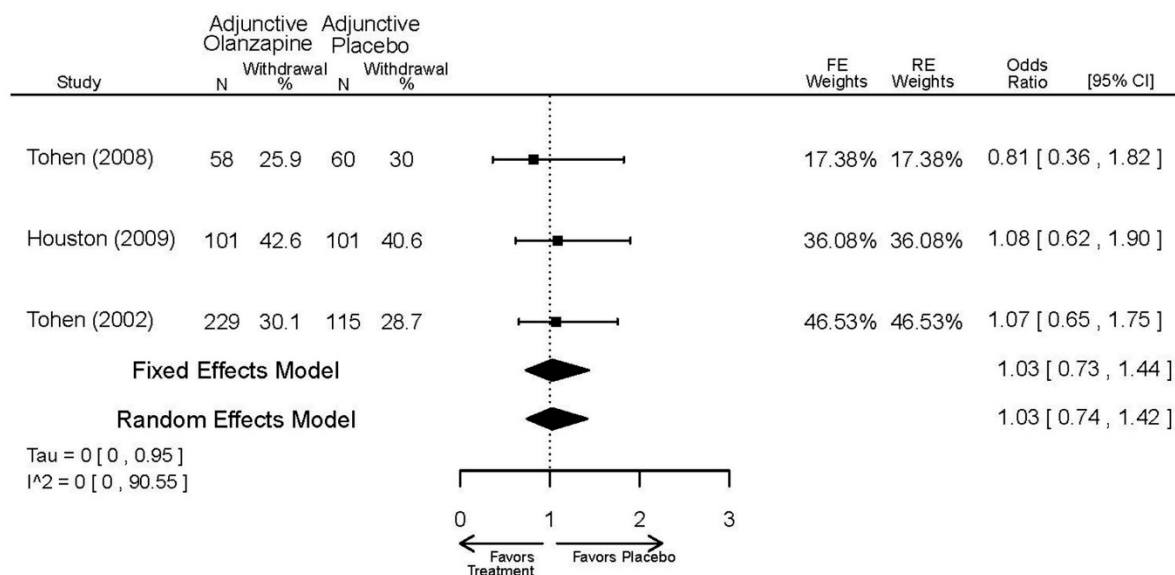
Appendix Figure E93. Adjunctive olanzapine vs. placebo – CGI

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to Last Measurement (6 Weeks)

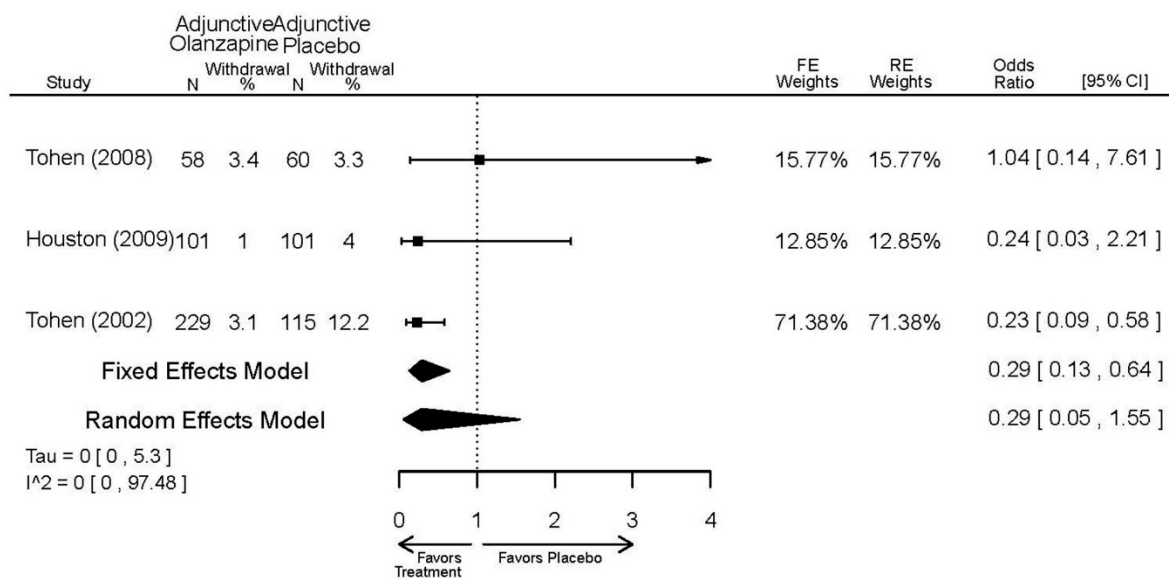


Appendix Figure E94. Adjunctive olanzapine vs. placebo – overall withdrawal

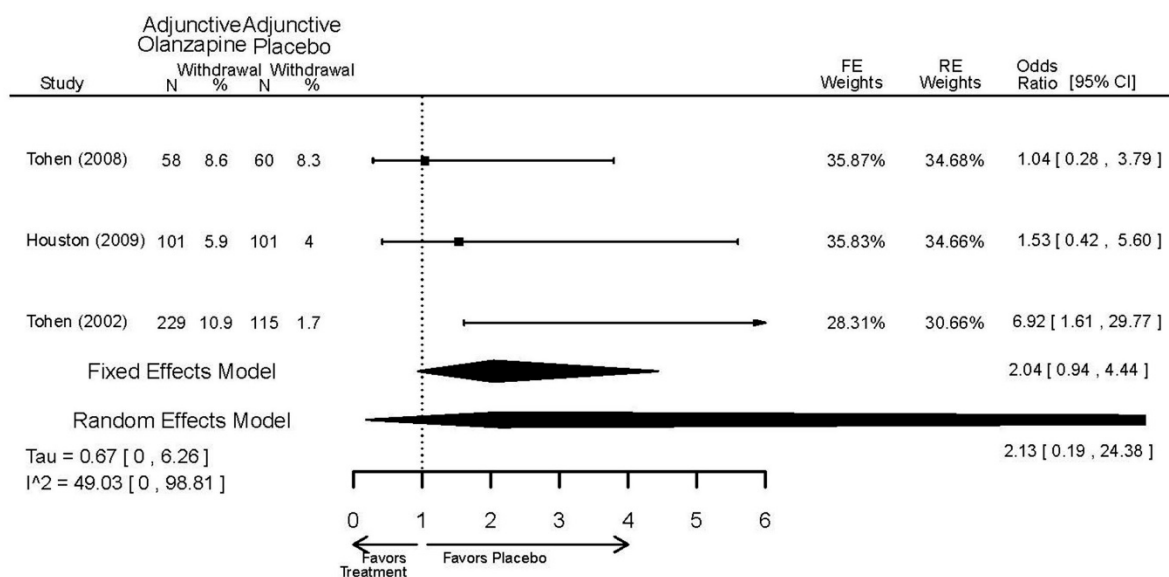
Odds Ratio of Withdrawal due to All Causes at Last Measurement (6 Weeks)



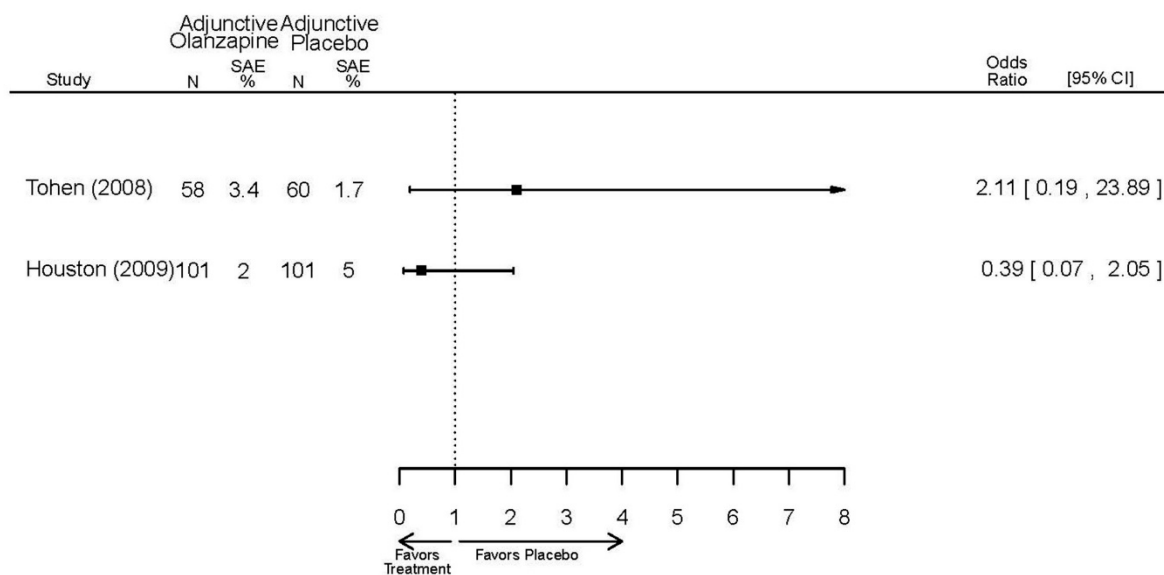
Appendix Figure E95. Adjunctive olanzapine vs. placebo – withdrawal – lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy
at Last Measurement (6 Weeks)



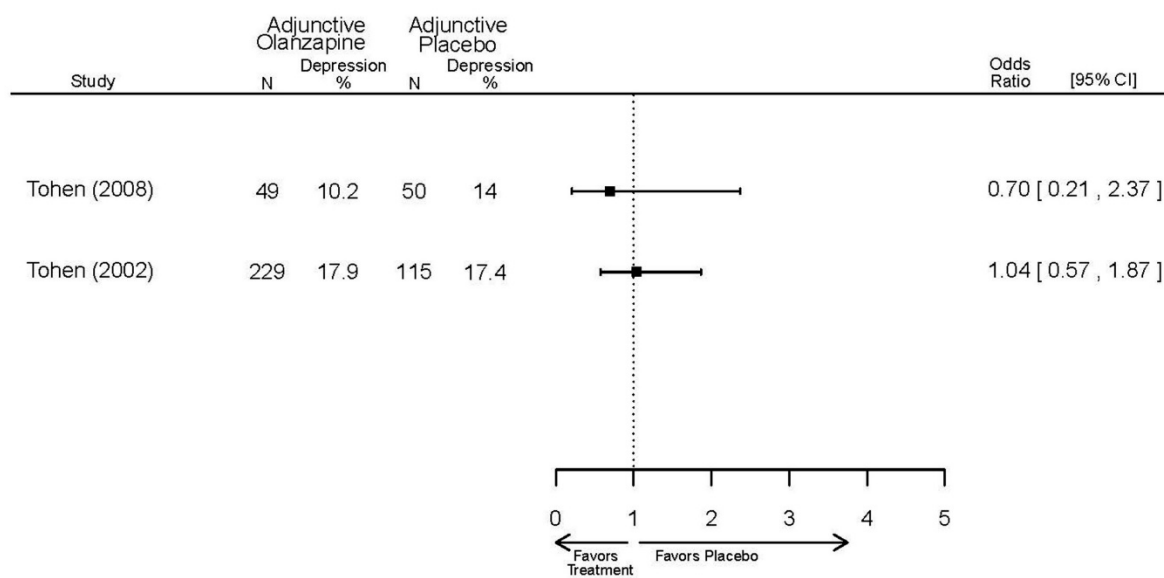
Appendix Figure E96. Adjunctive olanzapine vs. placebo – withdrawal – adverse events
Odds Ratio of Withdrawal due to Adverse Events
at Last Measurement (6 Weeks)



Appendix Figure E97. Adjunctive olanzapine vs. placebo – serious adverse events
Odds Ratio of Serious Adverse Event at Last Measurement (6 Weeks)

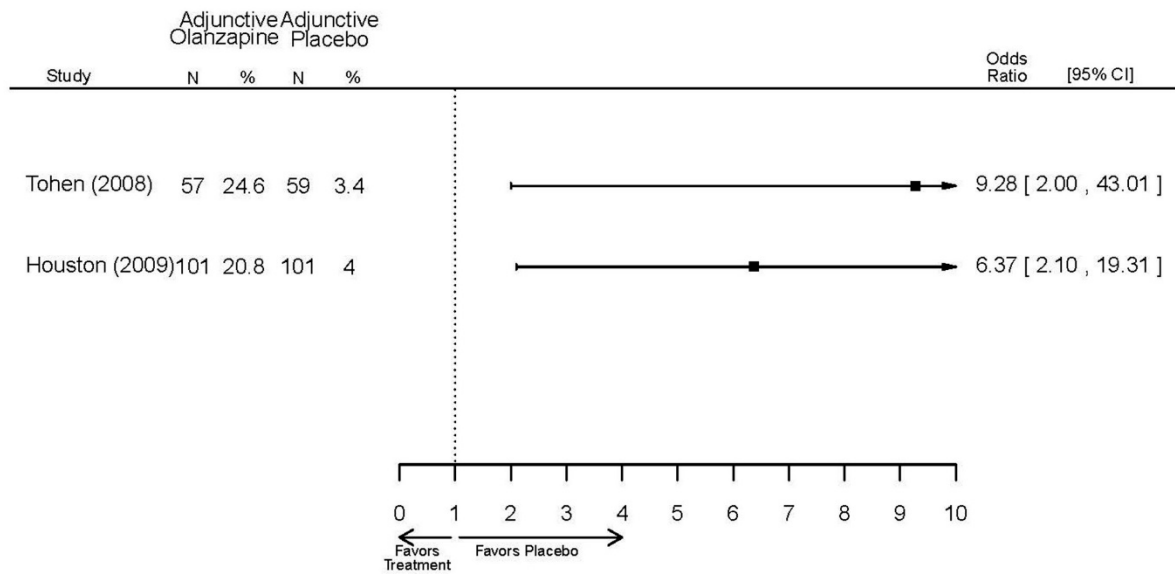


Appendix Figure E98. Adjunctive olanzapine vs. placebo – emergent depression last
Odds Ratio of Emergent Depression



Appendix Figure E99. Adjunctive olanzapine vs. placebo – weight

**Odds Ratio of Normalized Weight Change ($\geq 7\%$)
at Last Measurement (6 Weeks)**



Appendix Table E55. Outcomes summary: olanzapine plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Olanzapine adjunctive vs. chlorproma zine	Conus, 2015 ⁴⁷ 26485297 Low	<u>Symptomatic Recovery</u> 8 weeks Olanzapine=53.3% Chlorpromazine=54 .5% P=0.56 <u>Response</u> 8 weeks Olanzapine=96.7% Chlorpromazine=84 .8% P=0.12	<u>YMRS</u> 8 weeks Score ≤12 Olanzapine=93.3% Chlorpromazine=72.7 % P=0.03 Favors intervention <u>HAMD-21</u> 8 weeks Score <7 Olanzapine=53.3% Chlorpromazine=63.6 % P=0.28 NS	<u>GAF</u> 8 weeks NS No statistical test reported <u>QLS</u> 8 weeks NS No statistical test reported <u>PAS</u> 8 weeks NS No statistical test reported <u>CGI-BP</u> 8 weeks NS No statistical test reported	<u>ASI</u> 8 weeks NS No statistical test reported <u>Weight Gain</u> 8 weeks NS; p=0.22 <u>Overall Withdrawal</u> 8 weeks Olanzapine=4/42 Chlorpromazine=5/41 NS	<u>UKU</u> 8 weeks NS No statistical test reported <u>AE Leading to Trial Medication Interruption</u> 8 weeks Olanzapine=5.3% Chlorpromazine=6.8% NS P=0.47

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Olanzapine adjunctive vs. placebo or no placebo	Xu, 2015 ¹⁹ 26060401 Low	NR	YMRS 3 weeks Favors Olanzapine % Reduction (SD) Olanzapine+Valporate =86.5% (8.9%) Valproate=55.2% (5.7%) P<0.01 CGI-BP 3 weeks Difference in Difference (SE) 1.4 (0.53) Favors Olanzapine p<0.01	NR	<u>Overall Withdrawal</u> 3 weeks NS Olanzapine+Valporat e=2/40 Valproate=3/40 <u>Withdrawal due to AEs</u> 3 weeks NS Olanzapine+Valporat e=2/40 Valproate=0/40 <u>Withdrawal, Lack of Efficacy</u> 3 weeks NS Olanzapine+Valporat e=0/40 Valproate=2/40	<u>Severe Harms</u> 3 weeks NS Olanzapine+Valporate=1/38 Valproate=0/37 <u>Normalized Weight Change</u> 3 weeks Olanzapine+Valporate=31/38 Valproate=21/37 <u>Emergent Mood Episodes</u> 3 weeks NS Olanzapine+Valporate=0/38 Valproate=0/37
	Houston, 2009 ⁴⁸ 19778495 High	See forest plots E91 and E92 above	YMRS See forest plot E93 above	CGI-BP See forest plot E94 above	See forest plots E95, E96 and E97 above	<u>SAE</u> See forest plot E98 above <u>Deaths</u> 1 fatality from a car accident in the Olanzapine arm <u>Hepatic Failure</u> 1 case of acute hepatic failure in the Olanzapine arm Weight gain See forest plot E100 above

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
	Tohen, 2008 ⁴⁹ 18245032 Moderate	See forest plots E91 and E92 above	YMRS See forest plot E93 above MADRS 6 weeks Change (SE) Olanzapine -1.22 (0.96) Placebo -1.00 (0.96) NS	NR	See forest plots E95, E96 and E97 above	SAE See forest plots E98 aboveabove <u>Emergent depression</u> See forest plot E99 above Weight gain See forest plot E100 above
	Tohen, 2002 ⁵⁰ 11779284 High Baker, 2004 ⁵² 15572737 High Namijoshi, 2004 ⁵¹ 15337326 High	See forest plots E91 and E92 above	YMRS See forest plot E93 above	CGI-BP See forest plot E94 above	See forest plots E95, E96 and E97 above	SAE See forest plot E98 above EPS NS Emergent depression See forest plot E99 above

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E56. Strength of evidence assessment: olanzapine plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Olanzapine vs. Placebo/ adjunctive to Lithium or Valproate	6 weeks Remission Response YMRS CGI-BP Withdrawals	3 RCTs (n=664)	See table above	High	Consistent	Direct	Imprecise	Insufficient
Olanzapine vs. Placebo/ adjunctive to Carbamazepin e	Response Remission YMRS CGI-BP Withdrawals	1 RCT (n=118)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. No Placebo/ adjunctive to Divalproex/ Valproate	Response Remission YMRS CGI-BP Withdrawals	1 RCT (n=202)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. No Placebo/ adjunctive to Valproate	YMRS 3 weeks CGI-BP 3 weeks Withdrawals	1 RCT (n=80)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table E57. Outcomes summary: olanzapine plus mood stabilizers versus active comparison for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine adjunctive vs. chlorpromazine adjunctive	Conus, 2015 ⁴⁷ 26485297 Low	Response 8 weeks Olanzapine 94.7% Chlorpromazine 97.2% NS Remission 8 weeks Olanzapine 89.5% Chlorpromazine 88.9% NS	YMRS 8 weeks NS (data not reported) HAMD 8 weeks NS (data not reported)	CGI-BP-S 8 weeks NS (data not reported)	Withdrawal – Aes Olanzapine 26.3% Chlorpromazine 30.6% NS	SAE 3 chlorpromazine (extrapyramidal symptoms) 2 olanzapine (neutropenia, sedation) Weight gain NS

Abbreviations: AE=Adverse Events; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; HAMD=Hamilton Scale for Depression; NS=not significant; PMID=PubMed Identification Number; ROB=risk of bias; SAE; Serious Adverse Events; SE=standard error; YMRS = Young Mania Rating Scale

Appendix Table E58. Strength of evidence assessment: olanzapine plus mood stabilizers versus active comparison for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Olanzapine adjunctive vs. chlorpromazine adjunctive	Response Remission YMRS HAMD Withdrawal AE	1 RCT (n=83)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 12. Quetiapine Plus Mood Stabilizer

Appendix Table E59. Characteristics of eligible studies: quetiapine plus mood stabilizer drug treatments for acute mania by year then first author

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Yatham, 2007 ⁵³ RCT Multisite 4 Continents Industry RoB High 17519644	N = 200 Mean Age 40 Female 50% Race NR BP I 100% Inpatient (1 week) Outpatient (weeks 2-3, subject to inspector discretion)	Mania; YMRS ≥ 20 AND ≥ 4 on at least 2 YMRS subscales AND CGI-BP- S ≥ 4 First Manic Episode Taking Other Meds Pregnant/Nursing	Quetiapine 100-800 mg/day (455 mg/day mean) Adjunctive to Valproate 50-100 mcg/mL target OR Lithium 0.7-1.0 mEq/L target	Placebo Adjunctive to Valproate 50-100 mcg/mL target OR Lithium 0.7-1.0 mEq/L target	3 weeks	CGI-BP-S Remission (Various definitions) Response (YMRS 50% decrease) YMRS Withdrawal 36%
Yatham, 2004 ⁵⁴ RCT Multisite 4 Continents Industry RoB Moderate 15538120	N = 402 Mean Age 40 Female 47% Race NR BP I 100% Inpatient	Mania; At least one manic or mixed episode in previous 5 years. YMRS ≥ 20 , including score ≥ 4 on two core YMRS items; CGI-BP \geq 4 First Manic Episode Substance Abuse Other Mental Health Pregnant/Nursing	Quetiapine 100-800 mg/day (492 mg/day mean) Adjunctive to Valproate 50-100 mcg/mL target OR Lithium 0.7-1.0 mEq/L target	Placebo Adjunctive to Valproate 50-100 mcg/mL target OR Lithium 0.7-1.0 mEq/L target	6 weeks	YMRS CGI-BP PANSS MADRS GAS Adverse Events Withdrawals 38%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S= Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-

D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premord Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E60. Summary risk of bias assessments: quetiapine plus mood stabilizers for acute mania by year then first author

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Quetiapine	Yatham, 2007 ⁵³ Industry 17519644	High	Randomization and blinding not described. Improper definition of ITT "consisted of all the patients who had received at least one dose of study drug and had undergone a baseline AND at least one postbaseline efficacy assessment"; 2 patients missing from baseline quet. Measures, 9 patients missing from baseline placebo measures.
	Yatham, 2004 ⁵⁴ Industry 15538120	Moderate	Blinding and randomization not described; differential dropout rates between arms may alter effectiveness of randomization

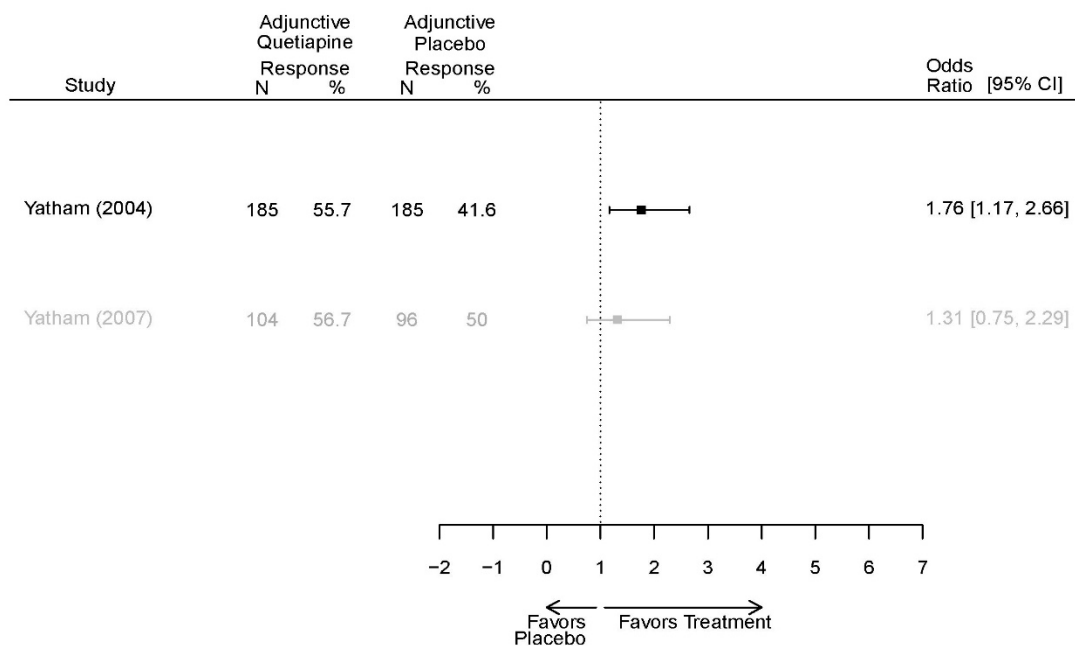
Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Antipsychotics Plus Mood Stabilizer Forest Plots

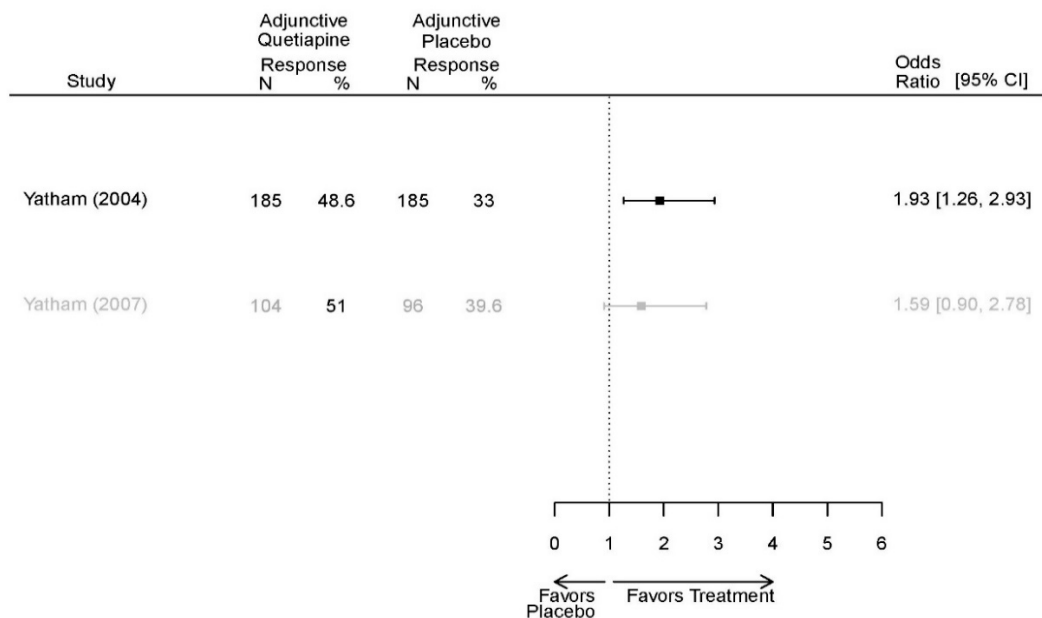
Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

Appendix Figure E100. Adjunctive Quetiapine vs. placebo – response

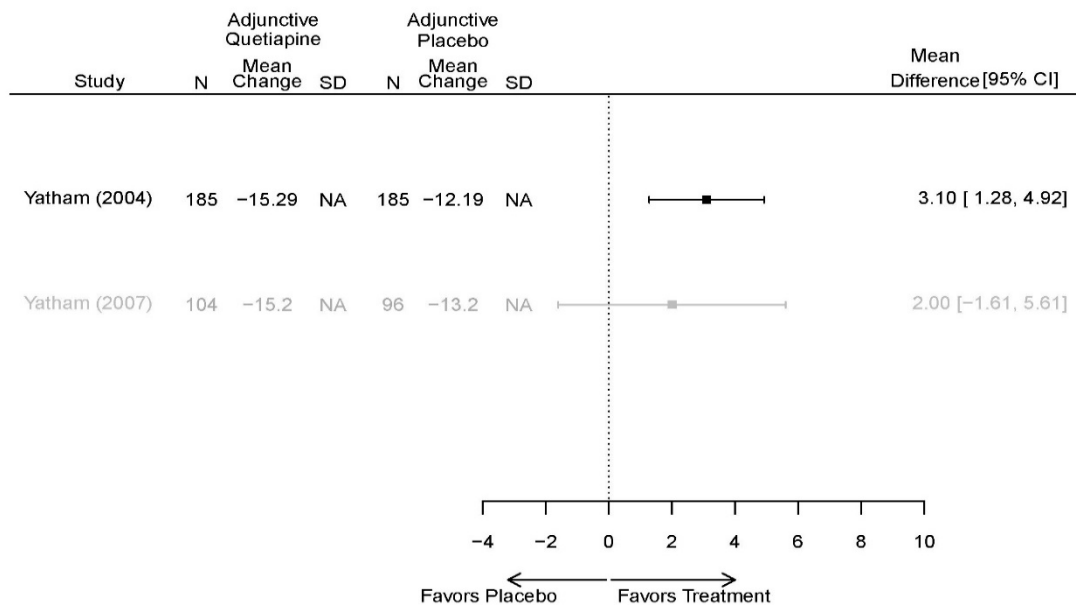
Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



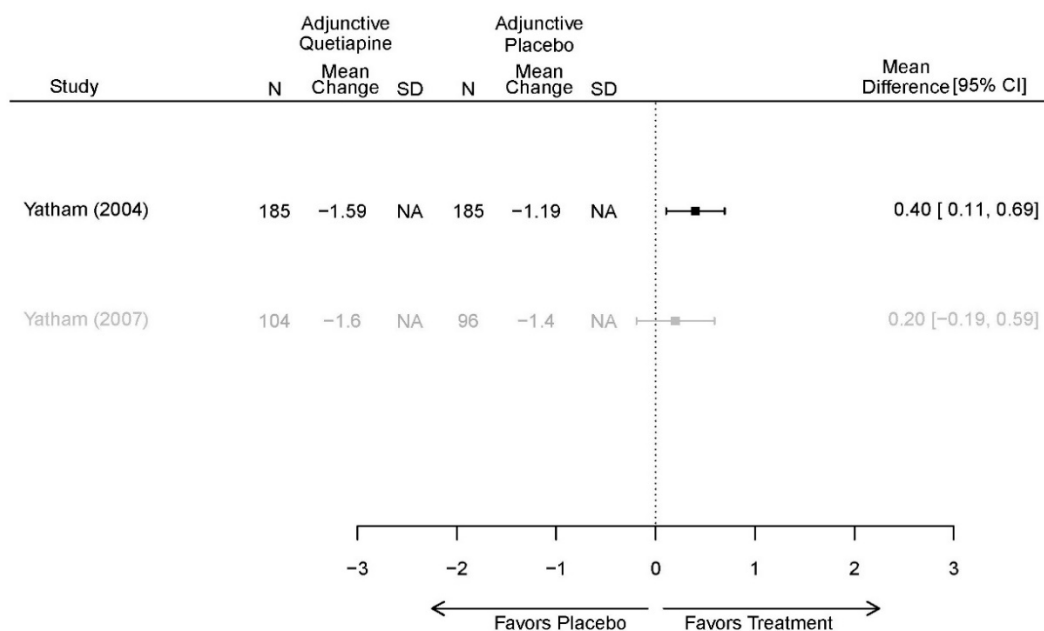
Appendix Figure E101. Adjunctive Quetiapine vs. placebo - remission
Odds Ratio of Remission (YMRS ≤ 12) at 3 Weeks



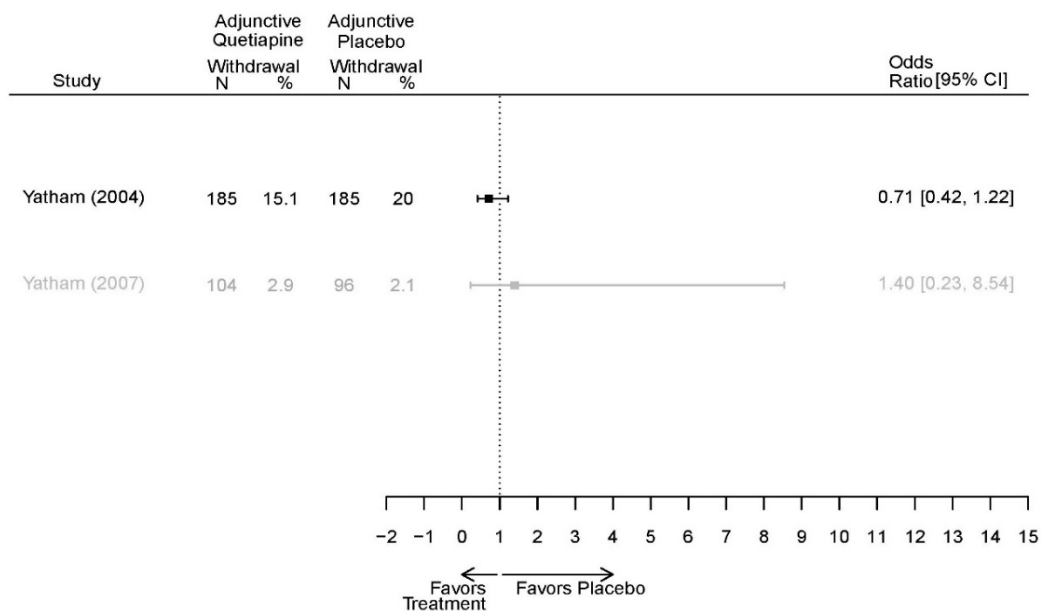
Appendix Figure E102. Adjunctive Quetiapine vs. placebo – YMRS
Difference in Mean Change in YMRS from Baseline to Last Measurement



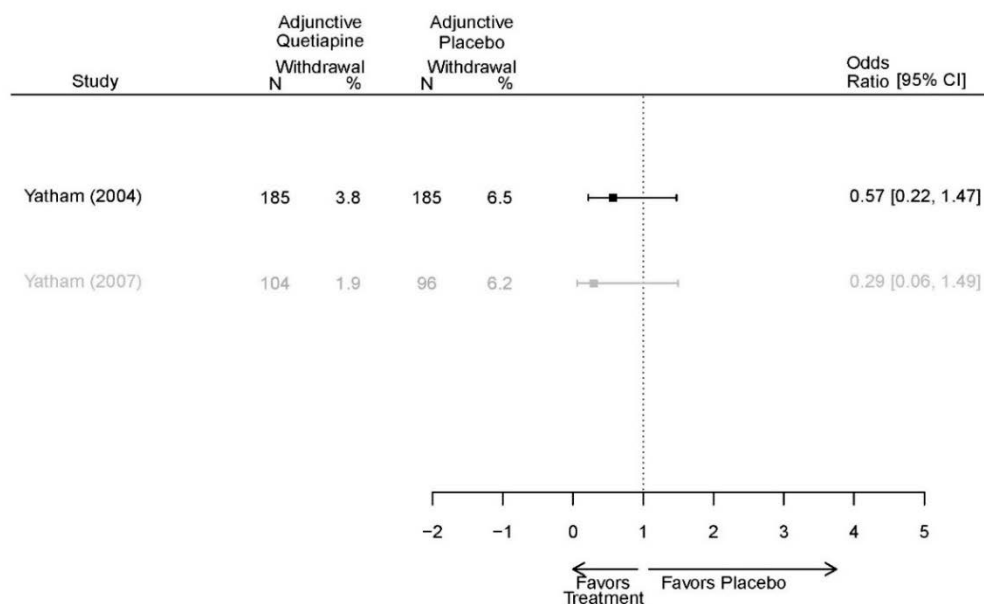
Appendix Figure E103. Adjunctive Quetiapine vs. placebo – CGI-BP-S
Difference in Mean Change in CGI-BP-S (Overall)
from Baseline to Last Measurement



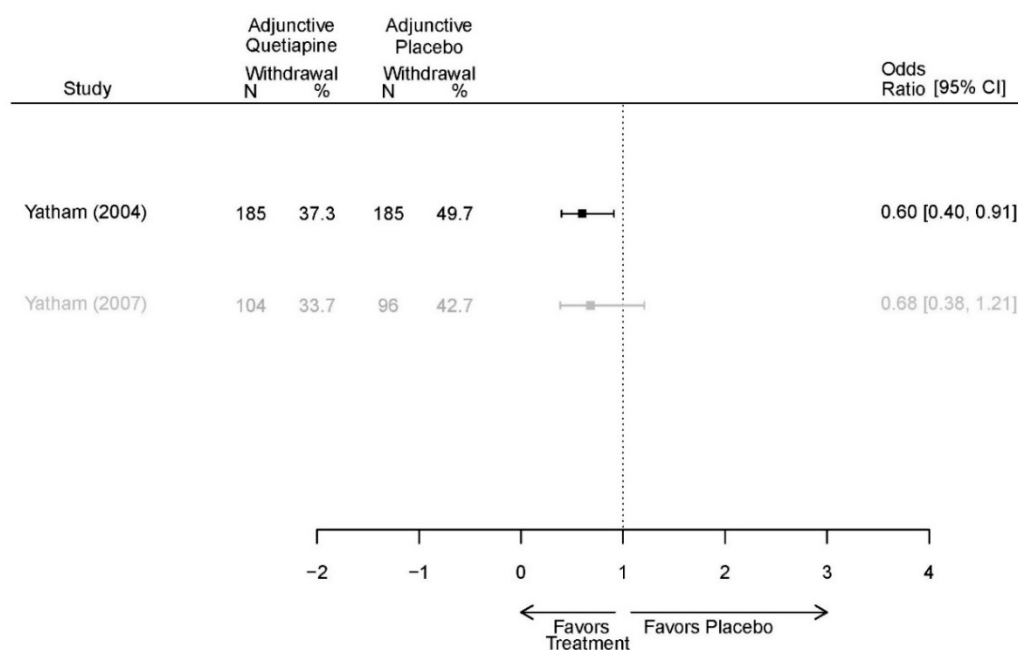
Appendix Figure E104. Adjunctive Quetiapine vs. placebo – withdrawal lack of efficacy
Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure E105. Adjunctive Quetiapine vs. placebo – withdrawal adverse events
Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Figure E106. Adjunctive Quetiapine vs. placebo – overall withdrawal
Odds Ratio of Overall Withdrawal



Appendix Table E61. Outcomes summary: quetiapine plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Quetiapine adjunctive vs. placebo	Yatham, 2007 ⁵³ 17519644 High	See forest plots E101 and E102 above	See forest plot E103 above	See forest plot E104 above	See forest plots E105, E106, and E107 above	<u>Serious Adverse Events</u> 6 weeks 1 placebo <u>Deaths</u> 6 weeks 1 placebo <u>EPS</u> 6 weeks 29.2% placebo 17.9% Quetiapine + Lithium
	Yatham, 2004 ⁵⁴ 15538120 Moderate	See forest plots E101 and E102 above	See forest plot E103 above	See forest plot E104 above	See forest plots E105, E106, and E107 above	<u>Serious Adverse Events</u> 6 weeks 0 in all arms <u>Deaths</u> 6 weeks 0 in all arms <u>EPS</u> 6 weeks 19.2% placebo 21.4% Quetiapine + Lithium

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E62. Strength of evidence assessment: quetiapine plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Quetiapine adjunctive vs. placebo	Response 3 wks Remission 3 wks YMRS 3 wks CGI-BP 3 wks Withdrawals	2 RCTs (n=570)	See forest plots above	High	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 13. Risperidone Plus Mood Stabilizer

Appendix Table E63. Characteristics of eligible studies: risperidone plus mood stabilizer drug treatments for acute mania by year then first author

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Yatham, 2003 ⁵⁵ RCT Multisite 4 Continents Industry RoB Low 12562742	N = 151 Mean Age 40 Female 58% Race NR Inpatient	Mania; YMRS ≥ 20 Schizoaffective Substance Abuse Other Mental Health Pregnant/Nursing Labs/Other Conditions	Risperidone 2-6 mg/day (Mean 4.0 mg/day) Adjunctive to Lithium or Divalproex or Carbamazepine	Placebo Adjunctive to Lithium or Divalproex or Carbamazepine	3 weeks	Response (YMRS 50% decrease) BPRS CGI HAM-D YMRS Withdrawal 44%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S== Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premordid Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E64. Summary risk of bias assessments: risperidone plus mood stabilizers for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Risperidone	Yatham, 2003 ⁵⁵ Industry 12562742	Low	A well described and reported study with some minor lack of disclosure in blinding procedure and adverse events reporting. 44% dropout.

Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Appendix Table E65. Outcomes summary: risperidone plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Risperidone adjunctive vs. placebo	Yatham, 2003 ⁵⁵ 12562742 Low	<u>Response, Mean Difference</u> 3 weeks 17.7% (95% CI 0.8- 33.5); p<0.05 Favors intervention	<u>YMRS, Mean Difference in Change Score</u> 3 weeks -4.2 (95% CI -7.60, 0.53); p=0.09 NS <u>HAM-D</u> 3 weeks NS No statistical test reported <u>BPRS, Mean Change</u> 3 weeks Risperidone=-10.1 Placebo=-4.8 p=0.01 Favors intervention	<u>CGI-BP, Mean Difference in Responders</u> 3 weeks 17.5% (95% CI 1.1- 33.9) Favors Intervention	<u>Overall Withdrawal</u> 3 weeks Risperidone=36% Placebo=52% Mean difference in completion rates=16% (95% CI 0.32, 31.68) Favors Intervention	<u>One or More AEs, Between Group Difference</u> 3 weeks 6% (95% CI -9.9, 21.9) NS <u>EPS Symptoms</u> 3 weeks Risperidone=16/75 Placebo=8/75 P=0.013

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E66. Strength of evidence assessment: risperidone plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Risperidone adjunctive vs. placebo	Response 3 wks YMRS 3 wks CGI-BP 3 wks Withdrawal – overall	1 RCT (n=150)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale
Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 14. Ziprazidone Plus Mood Stabilizer

Appendix Table E67. Characteristics of eligible studies: ziprasidone plus mood stabilizer drug treatments for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Sachs, 2012 ⁵⁶ RCT Multisite US Industry RoB High 23218157	N = 680 Mean Age 41 Female 50% White 65% BP I 100% Outpatient	Mania; YMRS ≥ 18 with 25% improvement between screening and baseline; current episode ≤ 3 months First manic episode Schizoaffective Substance Abuse Other Mental Health Conditions Taking Other Meds Labs/Other Conditions	Low Dose Ziprasidone (40-80 mg/day) Adjunctive to Lithium/Valproate OR High Dose Ziprasidone (120-160 mg/day) Adjunctive to Lithium/Valproate	Placebo Adjunctive to Lithium/Valproate	3 weeks	CGI-I CGI-S GAF LIFE-RIFT MADRS PANSS YMRS Withdrawal 42%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; ASI=Addiction Severity Index; BAS=Behavioral Approach System; BID=Twice a day; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI-BP=Clinical Global Impressions Scale, Bipolar; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S= Clinical Global Impressions-Severity Scale; DSM-IV-TR= Diagnostic and statistical manual, 4th edition, Text Revision; EPS=extrapyramidal symptoms; FAST=Functional Assessment Short Test; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HAMD-21=Hamilton Rating Scale for Depression (21-items); HDRS-21=Hamilton Depression Rating Scale (21-items); ISST=International Suicide Prevention Trial Scale for Suicidal Thinking; LIFE-RIFT=Longitudinal Interval Follow-up Evaluation-Rating Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; OR=Odds Ratio; PANSS=Positive and Negative Syndrome Scale; PAS=Premorbid Adjustment Scale; PGI-I=Patient Global Impression Improvement; PMID=PubMed Identification Number; QLS=Quality of Life Scale; RCT=randomized controlled trial; RDQ=Readiness to Discharge Questionnaire; ROB=risk of bias; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; SAS=Simpson Angus Scale; SF-36=36-Item Short Form Health Survey; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E68. Summary risk of bias assessments: ziprasidone plus mood stabilizers for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Ziprasidone	Sachs, 2012 ⁵⁶ Industry 23218157	High	Randomization and blinding not disclosed. Did not address how 680 were randomized but only 656 treated and analyzed. ITT noted, but they call this a modified ITT.

Abbreviations: ITT=intention to treat; PMID=PubMed Identification Number

Appendix Table E69. Outcomes summary: ziprasidone plus mood stabilizers versus placebo for acute mania

Drug	Study PMID RoB	Responder/ Remitter	Symptom	Function	Other	AE
Ziprasidone e adjunctive vs. placebo	Sachs, 2012 ⁵⁶ 23218157 High	NR	<u>YMRS Change</u> 3 week Low dose NS High dose NS	<u>CGI-S</u> 3 week Low dose NS High dose NS <u>GAF</u> 3 week Low dose NS High dose NS	<u>Overall Withdrawal</u> Low dose 48/226 High dose 62/232 Placebo 38/222 <u>Withdrawal Lack of efficacy</u> Low dose 6/226 High dose 4/232 Placebo 8/222 <u>Withdrawal Adverse event</u> Low dose 15/226 High dose 33/232 Placebo 11/222	SAE 11 ziprasidone groups 6 placebo EPS Low dose 1.9% High dose 4.9% Placebo 0.5%

Abbreviations: AE=Adverse Events; ASI=Addiction Severity Index; BPRS=Brief Psychiatric Rating Scale; CGI-Bp=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PAS=Premorbid Adjustment Scale; PMID=PubMed Identification Number; QLS=Quality of Life Scale; ROB=risk of bias; SAE=Serious Adverse Events; SE=Standard Error; UKU=UKU rating scale; YMRS = Young Mania Rating Scale

Appendix Table E70. Strength of evidence assessment: ziprasidone plus mood stabilizers versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Ziprasidone adjunctive vs. placebo	YMRS 3 wks CGI-BP 3 wks Withdrawal	1 RCT (n=680)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

References for Appendix E

1. Kanba S, Kawasaki H, Ishigooka J, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole for the treatment of acute manic or mixed episodes in Asian patients with bipolar I disorder (the AMAZE study). *The World Journal of Biological Psychiatry*. 2014 2014;15(2):113-21. doi: <http://dx.doi.org/10.3109/15622975.2012.669047>. PMID: 22540407.
2. Young AH, Oren DA, Lowy A, et al. Aripiprazole monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. *British Journal of Psychiatry*. 2009 Jan;194(1):40-8. doi: <http://dx.doi.org/10.1192/bjp.bp.108.049965>. PMID: 19118324.
3. Sachs G, Bowden C, Calabrese JR, et al. Effects of lamotrigine and lithium on body weight during maintenance treatment of bipolar I disorder. *Bipolar Disorders*. 2006 Apr;8(2):175-81. PMID: 16542188.
4. Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Current Medical Research & Opinion*. 2005 Jun;21(6):923-34. PMID: 15969892.
5. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. *Journal of Psychopharmacology*. 2006 Jul;20(4):536-46. PMID: 16401666.
6. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. *British Journal of Psychiatry*. 2005 Sep;187:235-42. PMID: 16135860.
7. Landbloom RL, Mackle M, Wu X, et al. Asenapine: Efficacy and safety of 5 and 10mg bid in a 3-week, randomized, double-blind, placebo-controlled trial in adults with a manic or mixed episode associated with bipolar I disorder. *Journal of Affective Disorders*. 2016 Jan 15;190:103-10. doi: <http://dx.doi.org/10.1016/j.jad.2015.06.059>. PMID: 26496015.
8. McIntyre RS. Aripiprazole for the maintenance treatment of bipolar I disorder: A review. *Clinical Therapeutics*. 2010;32 Suppl 1:S32-8. doi: <http://dx.doi.org/10.1016/j.clinthera.2010.01.022>. PMID: 20152551.
9. McIntyre RS, Cohen M, Zhao J, et al. A 3-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states.[Erratum appears in *Bipolar Disord*. 2010 May;12(3):350]. *Bipolar Disorders*. 2009 Nov;11(7):673-86. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00748.x>. PMID: 19839993.
10. Calabrese JR, Keck PE, Jr., Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 2015 Mar;76(3):284-92. doi: <http://dx.doi.org/10.4088/JCP.14m09081>. PMID: 25562205.
11. Durgam S, Starace A, Li D, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disorders*. 2015 Feb;17(1):63-75. doi: <http://dx.doi.org/10.1111/bdi.12238>. PMID: 25056368 (pubmed) 2014-30788-001(Psychinfo).
12. McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010 Apr;122(1-2):27-38. doi: <http://dx.doi.org/10.1016/j.jad.2009.12.028>. PMID: 20096936.
13. Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: a double-blind, placebo-controlled, phase III trial. *Journal of Affective Disorders*. 2015 Mar 15;174:296-302. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.018>. PMID: 25532076.
14. McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania--a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. *European Neuropsychopharmacology*. 2005 Oct;15(5):573-85. PMID: 16139175.

15. Smulevich AB, Khanna S, Eerdekens M, et al. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. *European Neuropsychopharmacology*. 2005 Jan;15(1):75-84. PMID: 15572276.
16. McIntyre RS, Cucchiaro J, Pikalov A, et al. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: post hoc analysis of a randomized placebo-controlled trial. *Journal of Clinical Psychiatry*. 2015 Apr;76(4):398-405. doi: <http://dx.doi.org/10.4088/JCP.14m09410>. PMID: 25844756.
17. Sachs GS, Grossman F, Ghaemi SN, et al. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *American Journal of Psychiatry*. 2002 Jul;159(7):1146-54. PMID: 12091192.
18. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disorders*. 2010 May;12(3):230-43. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00815.x>. PMID: 20565430.
19. Xu L, Lu Y, Yang Y, et al. Olanzapine-valproate combination versus olanzapine or valproate monotherapy in the treatment of bipolar mania: A randomized controlled study in a chinese population group. *Neuropsychiatric Disease and Treatment*. 2015 25 May;11:1265-71. doi: <http://dx.doi.org/10.2147/NDT.S81146>. PMID: 26060401 (pubmed) 2015078440 (embase).
20. Katagiri H, Takita Y, Tohen M, et al. Efficacy and safety of olanzapine in the treatment of Japanese patients with bipolar I disorder in a current manic or mixed episode: a randomized, double-blind, placebo- and haloperidol-controlled study. *Journal of Affective Disorders*. 2012 Feb;136(3):476-84. doi: <http://dx.doi.org/10.1016/j.jad.2011.10.045>. PMID: 22134043.
21. Vieta E, Suppes T, Ekholm B, et al. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. *Journal of Affective Disorders*. 2012 Dec 15;142(1-3):36-44. doi: <http://dx.doi.org/10.1016/j.jad.2012.04.014>. PMID: 23062763.
22. Niufan G, Tohen M, Qiuqing A, et al. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. *Journal of Affective Disorders*. 2008 Jan;105(1-3):101-8. PMID: 17531327.
23. Tohen M, Vieta E, Goodwin GM, et al. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *Journal of Clinical Psychiatry*. 2008 Nov;69(11):1776-89. PMID: 19014751.
24. Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *Journal of Clinical Psychiatry*. 2006 Apr;67(4):509-16. PMID: 16669715.
25. Revicki DA, Paramore LC, Sommerville KW, et al. Divalproex sodium versus olanzapine in the treatment of acute mania in bipolar disorder: health-related quality of life and medical cost outcomes. *Journal of Clinical Psychiatry*. 2003 Mar;64(3):288-94. PMID: 12716270.
26. Tohen M, Goldberg JF, Gonzalez-Pinto Arrillaga AM, et al. A 12-week, double-blind comparison of olanzapine vs haloperidol in the treatment of acute mania. *Archives of General Psychiatry*. 2003 Dec;60(12):1218-26. PMID: 14662554.
27. Shi L, Namjoshi MA, Zhang F, et al. Olanzapine versus haloperidol in the treatment of acute mania: clinical outcomes, health-related quality of life and work status. *International Clinical Psychopharmacology*. 2002 Sep;17(5):227-37. PMID: 12177585.
28. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania.[Erratum appears in *Am J Psychiatry*. 2005 Feb;7(1):102]. *American Journal of Psychiatry*. 2002 Jun;159(6):1011-7. PMID: 12042191.
29. Tohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzapine HGGW Study Group.[Erratum appears in *Arch Gen Psychiatry* 2002 Jan;59(1):91]. *Archives of General Psychiatry*. 2000 Sep;57(9):841-9. PMID: 10986547.
30. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. *International Clinical Psychopharmacology*. 1999 Nov;14(6):339-43. PMID: 10565800.

31. Katagiri H, Takita Y, Tohen M, et al. Safety and efficacy of olanzapine monotherapy and olanzapine with a mood stabilizer in 18-week treatment of manic/mixed episodes for Japanese patients with bipolar I disorder. *Current Medical Research & Opinion*. 2012 May;28(5):701-13. doi: <http://dx.doi.org/10.1185/03007995.2012.666961>. PMID: 22356118.
32. Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *European Neuropsychopharmacology*. 2012 Nov;22(11):825-35. doi: <http://dx.doi.org/10.1016/j.euroneuro.2012.03.004>. PMID: 22503488.
33. Shafti SS. Olanzapine vs. lithium in management of acute mania. *Journal of Affective Disorders*. 2010 May;122(3):273-6. doi: <http://dx.doi.org/10.1016/j.jad.2009.08.013>. PMID: 19740546.
34. Perlis RH, Baker RW, Zarate CA, Jr., et al. Olanzapine versus risperidone in the treatment of manic or mixed States in bipolar I disorder: a randomized, double-blind trial. *Journal of Clinical Psychiatry*. 2006 Nov;67(11):1747-53. PMID: 17196055.
35. Zajecka JM, Weisler R, Sachs G, et al. A comparison of the efficacy, safety, and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. *Journal of Clinical Psychiatry*. 2002 Dec;63(12):1148-55. PMID: 12523875.
36. Cutler AJ, Datto C, Nordenhem A, et al. Extended-release quetiapine as monotherapy for the treatment of adults with acute mania: a randomized, double-blind, 3-week trial. *Clinical Therapeutics*. 2011 Nov;33(11):1643-58. doi: <http://dx.doi.org/10.1016/j.clinthera.2011.10.002>. PMID: 22054797.
37. McElroy SL, Martens BE, Winstanley EL, et al. Placebo-controlled study of quetiapine monotherapy in ambulatory bipolar spectrum disorder with moderate-to-severe hypomania or mild mania. *Journal of Affective Disorders*. 2010 Jul;124(1-2):157-63. doi: <http://dx.doi.org/10.1016/j.jad.2009.11.014>. PMID: 19963274.
38. Li H, Ma C, Wang G, et al. Response and remission rates in Chinese patients with bipolar mania treated for 4 weeks with either quetiapine or lithium: a randomized and double-blind study. *Current Medical Research & Opinion*. 2008 Jan;24(1):1-10. PMID: 18028587.
39. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *Journal of Clinical Psychiatry*. 2005 Jan;66(1):111-21. PMID: 15669897.
40. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania. *The British Journal of Psychiatry*. 2005 2005;187(3):229-34. doi: <http://dx.doi.org/10.1192/bjp.187.3.229>. PMID: 16135859.
41. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clinical Neuropharmacology*. 1998 May-Jun;21(3):176-80. PMID: 9617509.
42. Potkin SG, Keck PE, Jr., Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *Journal of Clinical Psychopharmacology*. 2005 Aug;25(4):301-10. PMID: 16012271.
43. Keck PE, Jr., Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *American Journal of Psychiatry*. 2003 Apr;160(4):741-8. PMID: 12668364.
44. Jeong HG, Lee MS, Ko YH, et al. Combination treatment with aripiprazole and valproic acid for acute mania: an 8-week, single-blind, randomized controlled trial. *Clinical Neuropharmacology*. 2012 May-Jun;35(3):97-102. doi: <http://dx.doi.org/10.1097/WNF.0b013e3182560401>. PMID: 22592508.
45. Vieta E, T'Joens C, McQuade RD, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. *American Journal of Psychiatry*. 2008 Oct;165(10):1316-25. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.07101560>. PMID: 18381903.

46. Szegedi A, Calabrese JR, Stet L, et al. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *Journal of Clinical Psychopharmacology*. 2012 Feb;32(1):46-55. doi: <http://dx.doi.org/10.1097/JCP.0b013e31823f872f>. PMID: 22198448.
47. Conus P, Berk M, Cotton SM, et al. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: An 8-week randomised controlled trial. *European Psychiatry: the Journal of the Association of European Psychiatrists*. 2015 Nov;30(8):975-82. doi: <http://dx.doi.org/10.1016/j.eurpsy.2015.09.009>. PMID: 26485297.
48. Houston JP, Tohen M, Degenhardt EK, et al. Olanzapine-divalproex combination versus divalproex monotherapy in the treatment of bipolar mixed episodes: a double-blind, placebo-controlled study.[Erratum appears in *J Clin Psychiatry*. 2011 Aug;72(8):1157], [Erratum appears in *J Clin Psychiatry*. 2010 Jan;71(1):93]. *Journal of Clinical Psychiatry*. 2009 Nov;70(11):1540-7. doi: <http://dx.doi.org/10.4088/JCP.08m04895yel>. PMID: 19778495.
49. Tohen M, Bowden CL, Smulevich AB, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. *British Journal of Psychiatry*. 2008 Feb;192(2):135-43. doi: <http://dx.doi.org/10.1192/bjp.bp.107.041301>. PMID: 18245032.
50. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Archives of General Psychiatry*. 2002 Jan;59(1):62-9. PMID: 11779284.
51. Namjoshi MA, Risser R, Shi L, et al. Quality of life assessment in patients with bipolar disorder treated with olanzapine added to lithium or valproic acid. *Journal of Affective Disorders*. 2004;81(3):223-9. PMID: 15337326.
52. Baker RW, Brown E, Akiskal HS, et al. Efficacy of olanzapine combined with valproate or lithium in the treatment of dysphoric mania. *British Journal of Psychiatry*. 2004 Dec;185:472-8. PMID: 15572737.
53. Yatham LN, Vieta E, Young AH, et al. A double blind, randomized, placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. *International Clinical Psychopharmacology*. 2007 Jul;22(4):212-20. PMID: 17519644.
54. Yatham LN, Paulsson B, Mullen J, et al. Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania.[Erratum appears in *J Clin Psychopharmacol*. 2005 Apr;25(2):201], [Erratum appears in *J Clin Psychopharmacol*. 2005 Feb;25(1):103]. *Journal of Clinical Psychopharmacology*. 2004 Dec;24(6):599-606. PMID: 15538120.
55. Yatham LN, Grossman F, Augustyns I, et al. Mood stabilisers plus risperidone or placebo in the treatment of acute mania. International, double-blind, randomised controlled trial.[Erratum appears in *Br J Psychiatry*. 2003 Apr;182:369]. *British Journal of Psychiatry*. 2003 Feb;182:141-7. PMID: 12562742.
56. Sachs GS, Vanderburg DG, Edman S, et al. Adjunctive oral ziprasidone in patients with acute mania treated with lithium or divalproex, part 1: results of a randomized, double-blind, placebo-controlled trial. *Journal of Clinical Psychiatry*. 2012 Nov;73(11):1412-9. doi: <http://dx.doi.org/10.4088/JCP.11m07388>. PMID: 23218157.

Appendix F. Mood Stabilizers for Mania

Section 1. Carbamazepine

Appendix Table F1. Characteristics of eligible studies: carbamazepine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Weisler, 20061 2 pooled RCTs Multisite 2 Continents Industry RoB High 16529527 (pooled 15766298 and 15119909)	N = 443 Mean Age 38 Female 38% White 59% BP I 100% Inpatient or Outpatient	Manic/Mixed; YMRS \geq 20 Taking Other Meds	Carbamazepine ER 200-1600 mg/day (642.6 mg/day average)	Placebo	3 weeks	YMRS CGI-S CGI-I HAM-D Withdrawal 46%
Vasudev, 20002 RCT Singlesite India Industry RoB Moderate 10867972	N = 30 Age NR Sex NR Race NR BP I 100% Outpatient	Mania; DSM-III criteria for BP diagnosis Substance Abuse Neurological Disorders Taking other meds Pregnant/Nursing	Carbamazepine 800-1600 mg/day (22.05 mg/kg/day)	Valproate 800-2200 mg/day (22.9 mg/kg/day)	4 weeks	Response (50% decrease in YMRS) YMRS Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Small, 19913 RCT Singlesite US Government RoB High 1929761	N = 48 Mean Age 39 Female 38% White 59% BP I 100% Inpatient	Manic/Mixed; YMRS ≥ 20 First Manic Episode Substance Abuse Other Mental Health	Carbamazepine 700 mg/day-1052 mg/day (high and low weekly mean dose) (950.8 mg/day mean weekly dose)	Lithium 1035-1278 mg/day (high and low mean dose) (1207.5 mean weekly dose)	8 weeks	SDMS-D SDMS-M YMRS GAS CGI-I BCL Withdrawal 42%
Lerer, 19874 RCT Singlesite US Industry RoB High 3546274	N = 34 Mean Age 41 Female 54% Race NR BP I 100% Inpatient	Manic Neurological Disorders	Carbamazepine 600-2600 mg/day (1250 mg/day mean of the reported weekly median)	Lithium 900-3900 mg/day (1650 mg/day mean of the reported weekly median)	4 weeks	Response (CGI change 2+) CGI Withdrawal 18%

Abbreviations: AE=Adverse Events; AIMS=Abnormal Involuntary Movement Scale; BAS=Behavioral Approach System; BCL= Shopsin-Gershon Social Behavior Checklist; BIS-11=Barratt Impulsiveness Scale; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-I= Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSM-IV= Diagnostic and statistical manual, 4th edition; DSS=Depressive Syndrome Scale; ER=extended release; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; LIFE-RIFT= Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MSS=Manic Syndrome Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SADS-C=Schedule for Affective Disorders and Schizophrenia Change Version; SAS=Simpson Angus Scale; SDMS=Symptoms of Depression and Mania Scale; YMRS = Young Mania Rating Scale

Appendix Table F2. Summary risk of bias assessments: carbamazepine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Carbamazepine	Weisler, 2006 ¹ Industry 16529527	High	Large dropout rates (46%) with randomization and blinding not described.
	Vasudev, 2000 ² Industry 10867972	Moderate	Protection of allocation not described, but blinding and randomization are well addressed as are other aspects of the paper. Withdrawal 20%.
	Small, 1991 ³ Government 1929761	High	Randomization procedure and allocation masking not described. 42% dropout.
	Lerer, 1987 ⁴ Industry 3546274	High	The researcher only included in the analysis those who completed the study. This is likely to bias the results of the Lithium group who lost roughly 1/4 of the study population during the four weeks. Randomization procedure and allocation masking not described. 18% dropout.

Abbreviations: PMID=PubMed Identification Number

Appendix Table F3. Outcomes summary: carbamazepine versus placebo for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Carbamazepine vs. placebo	Weisler, 2006 ¹ 16529527 2 pooled RCTs (15766298 and 15119909) High	<u>Responders (>50% decrease YMRS)</u> 3 weeks Favors carbamazepine Carbamazepine 52% Placebo 26% p<0.0001	<u>YMRS decrease</u> 3 weeks Favors carbamazepine Carbamazepine 12.3 Placebo 6.2 p<0.0001 <u>HAM-D decrease</u> 3 weeks Favors carbamazepine Carbamazepine 2.9 Placebo 1.3 p=0.01	<u>CGI-S increase</u> 3 weeks Favors carbamazepine Carbamazepine 1.2 Placebo 0.5 p<0.0001 <u>CGI-I improvement</u> 3 weeks Favors carbamazepine Carbamazepine 55.6% Placebo 28.4% p<0.0001	<u>Overall Withdrawal</u> Carbamazepine 93/223 Placebo 110/220 NS <u>Withdrawal lack of effect</u> Carbamazepine 22/223 Placebo 49/220 Favors Carbamazepine <u>Withdrawal adverse events</u> Carbamazepine 24/223 Placebo 12/220 NR (EPC calculated favors carbamazepine) <u>BMI Change</u> Favors placebo ≥7% gain Carbamazepine 5.3% Placebo 1% p=0.011	<u>SAE</u> (from original studies) Carbamazepine: 8 patients Placebo: 10 patients Severe Rash: 11 carbamazepine patient 1 placebo patient attempted suicide

Abbreviations: AE=Adverse Effects; BMI=Body Mass Index; CGI= Clinical Global Impressions; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S=CGI-Severity; CI= Confidence Interval; EPS=Extrapyramidal Side Effects; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OPT=Optimalized Personalized Treatment; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE= Serious Adverse Events; SD=Standard Deviation; SE=Standard Error; YMRS = Young Mania Rating Scale

Appendix Table F4. Strength of evidence assessment: carbamazepine versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Carbamazepine vs. placebo	Response YMRS CGI Withdrawals	1 RCT + 1 IPD (n=443)	See table above	High	Consistent (based on original RCTs)	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Events; CGI= Clinical Global Impressions; CI=Confidence Interval; IPD=Individual patient data; MADRS=Montgomery-Asberg Depression Rating Scale; MD=Mean Difference; NS=Not Significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table F5. Outcomes summary: carbamazepine versus active comparator for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Carbamazepine vs. lithium	Small, 1991 ³ 1929761 High	NR	<u>YMRS</u> 8 weeks Carbamazepine -8.5 Lithium -9.7 4% difference between groups <u>HAM-D</u> 8 weeks Carbamazepine -2.5 Lithium 0.5 10% difference between groups <u>SDMS-D</u> 8 weeks Carbamazepine 0 Lithium 0.6 18% difference between groups <u>SDMS-M</u> 8 weeks Carbamazepine -3.4 Lithium -3.3 1% difference between groups	<u>CGI-I</u> 8 weeks Carbamazepine -0.9 Lithium 1.0 1% difference between groups <u>GAS</u> 8 weeks Carbamazepine 11.7 Lithium 11.8 3% difference between groups	<u>Overall Withdrawal</u> Carbamazepine 16/24 Lithium 16/24 NS	<u>SAE</u> None
	Lerer, 1987 ⁴ 3546274 High	<u>Response (CGI change 2+)</u> 4 weeks Favors lithium Carbamazepine 4/14 Lithium 11/14 p<0.05	NR	<u>CGI</u> Carbamazepine Baseline 5.6(8.2) 4 weeks 4.1 (1.51) Lithium Baseline 5.7(0.88) 4 weeks 3.1(1.5) ANOVA group effect NS	<u>Overall Withdrawal</u> Carbamazepine 1/15 Lithium 4/19 NR <u>Withdrawal adverse events</u> Carbamazepine 1/15 Lithium 2/19 NR	<u>SAE</u> Carbamazepine 4/15 Lithium 1/19

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Carbamazepine vs. valproate	Vasudev, 2000 ² 10867972 Moderate	<u>Response</u> (50% decrease in YMRS) 4 weeks Carbamazepine 8/15 Valproic acid 11/15 NS	NR	NR	<u>Overall Withdrawal</u> Carbamazepine 3/15 Valproic acid 3/15 NS	<u>All AEs</u> Carbamazepine 67% Valproic acid 17% <u>Tremors</u> Carbamazepine 25% Valproic acid 8%

Abbreviations: AE=Adverse Effects; BPRS=Brief Psychiatric Rating Scale; CGI= Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I=Clinical Global Impressions Scale-Improvement; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; MRS=mania rating scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE= Serious Adverse Events; SD=standard deviation; SDMS-D=Symptoms of Depression and Mania Scale-Depression; YMRS = Young Mania Rating Scale

Appendix Table F6. Strength of evidence assessment: carbamazepine versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Carbamazepine vs. lithium	Response YMRS CGI Withdrawals – overall Withdrawal – AEs	2 RCTs (n=82)	See table above	High	Consistent	Direct	Imprecise	Insufficient
Carbamazepine vs. valproate	Response Withdrawals – overall	1 RCT (n=30)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Event; CGI=Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; n=number; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 2. Divalproex/Valproate

Appendix Table F7. Characteristics of eligible studies: divalproex for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2008b ⁵ RCT Multisite 3 Continents Industry RoB Low 19014751	N = 521 Mean Age 40 Female 49% Race NR Diagnosis NR Setting NR	Manic or Mixed Episode; YMRS 20-30 CGI-BP mania 3-4 Schizoaffective Other Mental Health Conditions Pregnant/Nursing	Divalproex 500-2500 mg/day	C1: Placebo C2: Olanzapine 5-20 mg/day	3 weeks	Response (YMRS reduction $\geq 50\%$) Time to response (days from baseline to $\geq 50\%$ YMRS reduction) Remission (YMRS \leq 12) Efficacy YMRS CGI (multiple subscales) MADRS Adverse events Extrapyramidal symptoms SAS BAS AIMS Withdrawal 26%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Bowden, 2006 ⁶ RCT Multisite US Industry RoB High 17107240	N = 364 Mean Age 38 Female 43% White 74% BP I 100% Inpatient (0-15 days) Outpatient (>15-21 days, subject to clinical criteria)	Mania; Mania Rating Scale (derived from SADS-C interview) ≥ 18 with at least 4 item scores >1. First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health Conditions; Taking other Medications;	Divalproex 85-125 microgram/ml (2961 mg/day average)	Placebo	3 weeks	Remission (YMRS ≤ 12) Response (50% decrease in YMRS) YMRS BIS MSS GAS DSS AEs Weight gain Withdrawal 45%
Xu, 2015 ⁷ RCT Single-site China Government RoB Low 26060401	N = 120 Mean Age 31 Female 52% Race NR BP I 100% Setting NR	First manic; YMRS ≥17	Olanzapine 10 mg/day + Valproate 600 mg/day	C1: Olanzapine 10 mg/day Flexible dosing 5-20 mg/day C2: Valproate 600 mg/day alone	4 weeks	Efficacy YMRS CGI-BP Adverse events Extrapyramidal symptoms SAS Withdrawal 5%

Abbreviations: AE=Adverse Events; AIMS=Abnormal Involuntary Movement Scale; BAS=Behavioral Approach System; BCL= Shopsin-Gershon Social Behavior Checklist; BIS-11=Barratt Impulsiveness Scale; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-I= Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSM-IV= Diagnostic and statistical manual, 4th edition; DSS=Depressive Syndrome Scale; ER=extended release; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; LIFE-RIFT= Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MSS=Manic Syndrome Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SADS-C=Schedule for Affective Disorders and Schizophrenia Change Version; SAS=Simpson Angus Scale; SDMS=Symptoms of Depression and Mania Scale; YMRS = Young Mania Rating Scale

Appendix Table F8. Summary risk of bias assessments: dival/valproate for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Divalproex / Valproate	Tohen, 2008 ⁵ Industry 19014751	Low	No sources of bias identified. 26% dropout at 3 weeks.
	Bowden, 2006 ⁶ Industry 17107240	High	Randomization and allocation procedures not described. Author notes, "We plan to report in a separate article a detailed exploration of the site-related differences and the implications for study design and execution" This statement infers that there is a difference caused by site that is not addressed or controlled for in the paper. 45% dropout.
	Xu, 2015 ⁷ Government 26060401	Low	Well-constructed, described, and reported study. 5% dropout.

Abbreviations: PMID=PubMed Identification Number

Appendix Table F9. Outcomes summary: divalproex/valproate versus placebo for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Divalproex vs. placebo	Bowden, 2006 ⁶ 17107240 High	<u>Response</u> 3 weeks Favors divalproex Divalproex 48% Placebo 34% p=0.012 <u>Remission</u> 3 weeks Favors divalproex Divalproex 48% Placebo 35% p=0.015	<u>MRS Change</u> 3 weeks Favors divalproex Divalproex -11.5 Placebo -9.0 p=0.013	<u>GAS</u> 3 weeks NS	<u>Overall Withdrawal</u> Divalproex 108/187 Placebo 92/177 NS <u>Withdrawal lack of effect</u> Divalproex 24/187 Placebo 46/177 Favors Divalproex p=0.001 <u>Withdrawal adverse events</u> Divalproex 19/187 Placebo 5/177 Favors Placebo p=0.003	<u>Serious Adverse Events</u> 3 weeks 1 in divalproex 0 in placebo <u>Deaths</u> 3 weeks 0 in both arms

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
	Tohen, 2008 ⁵ 19014751 Low	<u>Response</u> 3 weeks Divalproex 40.3% Placebo 31.3% NS <u>Remission</u> 3 weeks Divalproex 40.3% Placebo 35.4% NS	<u>YMRS Change</u> 3 weeks Divalproex -8.2 (SE 0.62) Placebo -7.4 (SE 0.80) NS	<u>CGI Overall Change</u> 3 weeks Divalproex -0.6 (SE 0.08) Placebo -0.5 (SE 0.10) NS <u>CGI Mania Change</u> 3 weeks Divalproex -0.8 (SE 0.08) Placebo -0.7 (SE 0.11) NS <u>CGI Depression Change</u> 3 weeks Divalproex -0.2 (SE 0.07) Placebo -0.1 (SE 0.09) NS	<u>Withdrawal</u> 3 weeks Overall: 25.5% Efficacy: 2.0% AEs: 2.3%	<u>Serious Adverse Events</u> 3 weeks 1 in divalproex 1 in placebo

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Valproate adjunctive vs. placebo or no placebo	Xu, 2015 ⁷ 26060401 Low	NR	YMRS 3 weeks Favors Valproate % Reduction (SD) Olanzapine+Valporate= 86.5% (8.9%) Olanzapine= 75.2% (15.1%) P<0.01 <u>CGI-BP</u> 3 weeks Favors Valproate p<0.01	NR	<u>Overall Withdrawal</u> 3 weeks NS Olanzapine + Valporate = 2/40 Olanzapine=1/40 <u>Withdrawal due to AEs</u> 3 weeks NS Olanzapine+Valporate=2/40 Olanzapine=1/40 <u>Withdrawal, Lack of Efficacy</u> 3 weeks NS Olanzapine+Valporate=0/40 Olanzapine=0/40	<u>Severe Harms</u> 3 weeks NS Olanzapine+Valporate=1/38 Olanzapine=0/39 <u>Normalized Weight Change</u> 3 weeks Olanzapine+Valporate=31/38 Olanzapine=29/39 <u>Emergent Mood Episodes</u> 3 weeks NS Olanzapine+Valporate=0/38 Olanzapine=0/39

Abbreviations: AE=Adverse Effects; BMI=Body Mass Index; CGI= Clinical Global Impressions; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S=CGI-Severity; CI= Confidence Interval; EPS=Extrapyramidal Side Effects; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OPT=Optimalized Personalized Treatment; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE= Serious Adverse Events; SD=Standard Deviation; SE=Standard Error; YMRS = Young Mania Rating Scale

Appendix Table F10. Strength of evidence assessment: divalproex/valproate versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Divalproex vs. placebo	Relapse Remission YMRS CGI Withdrawals	2 RCTs (n=670)	See table above	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Valproate vs. no placebo	YMRS CGI Withdrawals	1 RCT (n=79)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Events; CGI= Clinical Global Impressions; CI=Confidence Interval; IPD=Individual patient data; MADRS=Montgomery-Asberg Depression Rating Scale; MD=Mean Difference; NS=Not Significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 3. Lamotrigine

Appendix Table F11. Characteristics of eligible studies: lamotrigine for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Ichim, 2000 ⁸ RCT Singesite South Africa Industry RoB Moderate 10798820	N=30 Mean Age 33 Female 47% Race NR BP I 100% Inpatient	Mania Substance Abuse Taking Other Meds Pregnant/Nursing Labs/Other Conditions	Lamotrigine Week 1 25mg/day, Week 2 50mg/day, Week 3 100mg/day	Lithium 400mg twice/daily	4 weeks	YMRS BPRS CGI GAF Withdrawal 17%

Abbreviations: AE=Adverse Events; AIMS=Abnormal Involuntary Movement Scale; BAS=Behavioral Approach System; BCL= Shopsin-Gershon Social Behavior Checklist; BIS-11=Barratt Impulsiveness Scale; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-I= Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSM-IV= Diagnostic and statistical manual, 4th edition; DSS=Depressive Syndrome Scale; ER=extended release; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; LIFE-RIFT= Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MSS=Manic Syndrome Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SADS-C=Schedule for Affective Disorders and Schizophrenia Change Version; SAS=Simpson Angus Scale; SDMS=Symptoms of Depression and Mania Scale; YMRS = Young Mania Rating Scale

Appendix Table F12. Summary risk of bias assessments: lamotrigine for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lamotrigine	Ichim, 20008 Industry 10798820	Moderate	Randomization and blinding procedures not described. Initial difference between the two groups identified on duration since index episode before hospitalization.

Abbreviations: PMID=PubMed Identification Number

Appendix Table F13. Outcomes summary: lamotrigine versus active comparator for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Lamotrigine vs. Lithium	Ichim, 2000 ⁸ Moderate 10798820	<u>Response</u> 4 weeks NS Lamotrigine=8/15 Lithium=9/15	<u>YMRS</u> 4 weeks NS Lamotrigine=14.3 Lithium=13.2 <u>BPRS</u> 4 weeks NS Lamotrigine=30.2 Lithium=28.2	<u>CGI-Severity</u> 4 weeks NS Lamotrigine=2.77 Lithium=2.87 <u>CGI-Improvement</u> 4 weeks NS <u>GAF</u> 4 weeks NS Lamotrigine=55.7 Lithium=56.2	<u>Overall Withdrawal</u> 4 weeks NS 17% Lamotrigine=2/15 Lithium=3/15	<u>Serious AEs</u> 4 weeks No serious AEs reported in either group and no rashes were reported in the lamotrigine group.

Abbreviations: AE=Adverse Effects; BPRS=Brief Psychiatric Rating Scale; CGI= Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I=Clinical Global Impressions Scale-Improvement; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; MRS=mania rating scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE= Serious Adverse Events; SD=standard deviation; SDMS-D=Symptoms of Depression and Mania Scale-Depression; YMRS = Young Mania Rating Scale

Appendix Table F14. Strength of evidence assessment: lamotrigine versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lamotrigine vs. lithium	Response Withdrawals – overall	1 RCT (n=30)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Event; CGI=Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; n=number; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 4. Lithium

Appendix Table F15. Characteristics of eligible studies: lithium for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kushner, 2006 ⁹ RCT Multisite 4 Continents Industry RoB Low 16411977	N = 876 (includes only 400 mg/day topiramate arms and placebo arms Mean Age 41 Female (%) 51 White (%) 75 BP I (%) 100 Inpatient (at least 4 days, as clinically warranted)	Mania; YMRS ≥ 20 Schizoaffective; Substance Abuse; Other Mental Health Conditions; Taking Other Medications;	Topiramate 400mg/day (mean 313mg/day) (only 400 mg/day arms were common across pooled studies)	C1: Placebo n=427 C2: Lithium 300-1800 mg/day (0.8-1.2mEq/L) n=227	3 weeks	YMRS Weight BPRS CGI-S GAS Withdrawal 26%
Bowden, 2005 ¹⁰ RCT Multisite 2 Continents Industry RoB High 15669897	N=302 Mean Age 39 Female 42% Race NR BP I 100% Inpatient (week 1) Outpatient (weeks 2-12, subject to inspector discretion)	Mania; YMRS ≥ 20 including score of at least 4 on 2 of the 4 double-weighted items (irritability, speech, content, and disruptive/aggressive behavior), CGI ≥ 4 First manic episode; Substance Use; Taking other medications; Pregnant/Nursing; Labs/Other Conditions	Lithium 0.6-1.4 mEq/L (mean 0.80 mEq/L)	C1: Placebo C2: Quetiapine 100-800mg/day	12 weeks	CGI-BP-S GAS Remission YMRS ≤ 12) Response ($\geq 50\%$ YMRS decrease) Withdrawal 43%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Segal, 1998 ¹¹ RCT Singesite South Africa Industry/ University RoB Moderate 9617509	N=45 Mean Age 34 Female 78% Race NR BP I 100% Inpatient	Mania; DSM-IV criteria for Bipolar Manic Phase Substance Abuse; Taking other Medications; Pregnant/Nursing; Abnormal Lab Results	Lithium 0.6-1.2 mmol/L (Mean 0.72 mmol/L)	C1: Placebo C2: Haloperidol 10 mg/day	4 weeks	BPRS CGI Unknown Scale - Not reported whether global improvement or severity scale is being reported GAF MRS Seclusion – Hours Seclusion - Proportion of patients needing SAS Withdrawal 13%
Bowden, 2010 ¹² RCT Multisite 2 Continents Industry RoB Moderate 20101186	N = 270 Mean Age 39 Female 59% Race NR BP I 100% Inpatient and Outpatient	Mania; YMRS ≥ 18 First Manic Episode Substand Abuse Pregnant/Nursing Labs/Other Conditions Other Mental Health	Lithium 0.6-1.2 mmol/L (mean 969 mg/day)	Valproate 70-125 mcg/ml (mean 1394 mg/day)	12 weeks	CGI-BP-S Remission (YMRS ≤12 and decrease in CGI-BP ≥ 2) Remission (YMRS ≤ 12 and no increase in MADRS total score OR YMRS ≤ 12 and CGI ≤ 2 points) Response (improvement in YMRS ≥30%) YMRS Withdrawal 28%

Abbreviations: AE=Adverse Events; AIMS=Abnormal Involuntary Movement Scale; BAS=Behavioral Approach System; BCL= Shopsin-Gershon Social Behavior Checklist; BIS-11=Barratt Impulsiveness Scale; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-I= Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSM-IV= Diagnostic and statistical manual, 4th edition; DSS=Depressive Syndrome Scale; ER=extended release; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; LIFE-RIFT= Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MSS=Manic Syndrome Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number;

RCT=randomized controlled trial; ROB=risk of bias; SADS-C=Schedule for Affective Disorders and Schizophrenia Change Version; SAS=Simpson Angus Scale; SDMS=Symptoms of Depression and Mania Scale; YMRS = Young Mania Rating Scale

Appendix Table F16. Summary risk of bias assessments: lithium for acute mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lithium	Bowden, 2010 ¹² Industry 20101186	Moderate	Randomization procedure not described, patients and raters may not be blinded. 28% dropout.
	Kushner, 2006 ⁹ Industry 16411977	Low	No sources of bias identified
	Bowden, 2005 ¹⁰ Industry 15669897	High	Randomization and blinding not described. Overall dropout of 43%.
	Segal, 1998 ¹¹ Industry/ University 9617509	Moderate	Noted 'randomly and assigned consecutively to treatment with...' which is a pseudorandom assignment technique. Blinding not described.

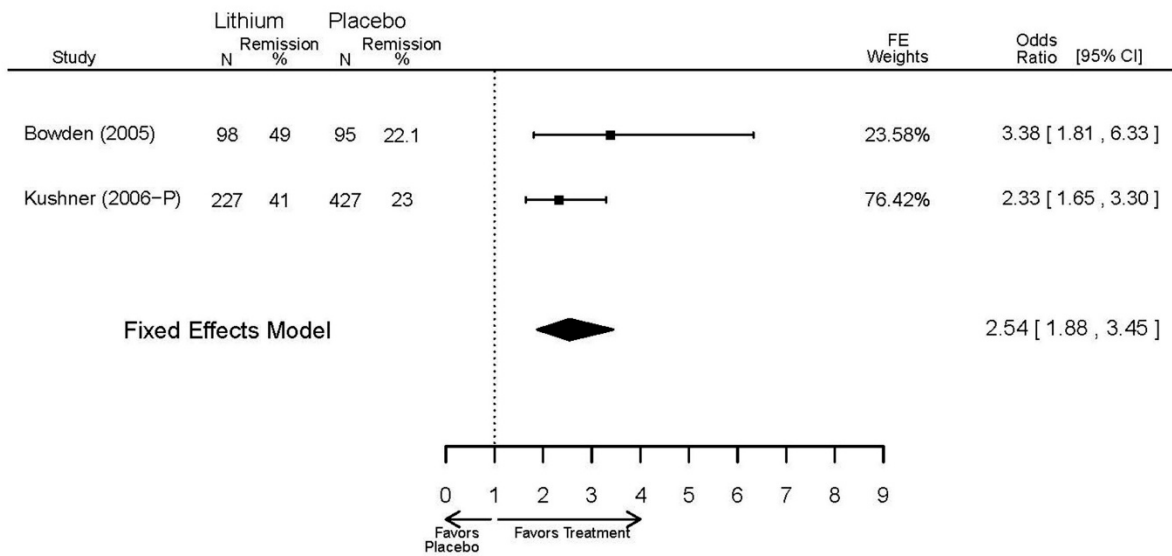
Abbreviations: PMID=PubMed Identification Number

Mood Stabilizer Forest Plots

Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

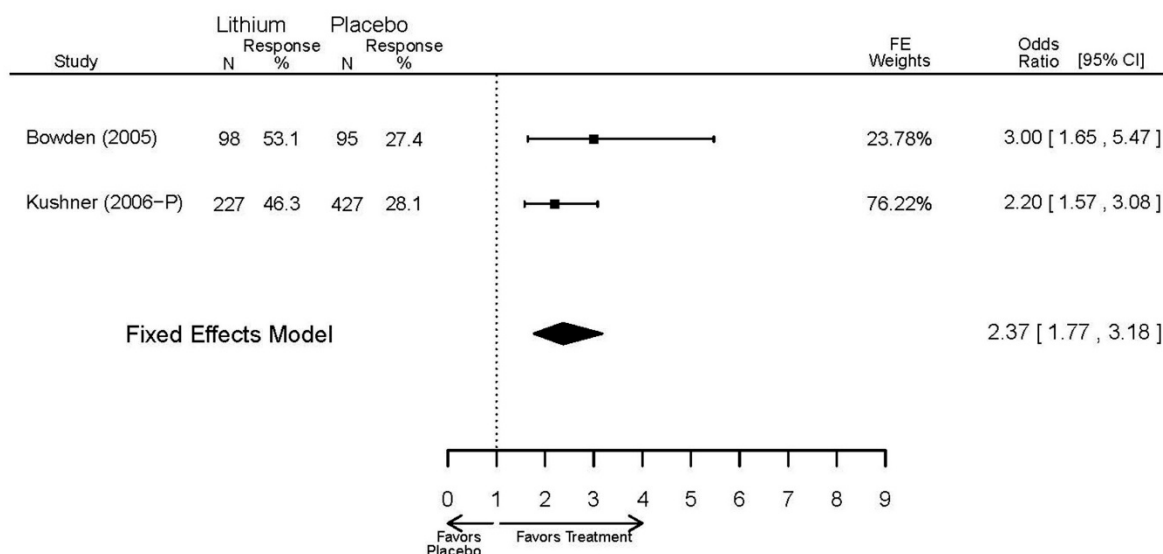
Appendix Figure F1. Lithium vs. placebo – remission

Odds Ratio of Remission (YMRS 12 or Less) at 3 Weeks



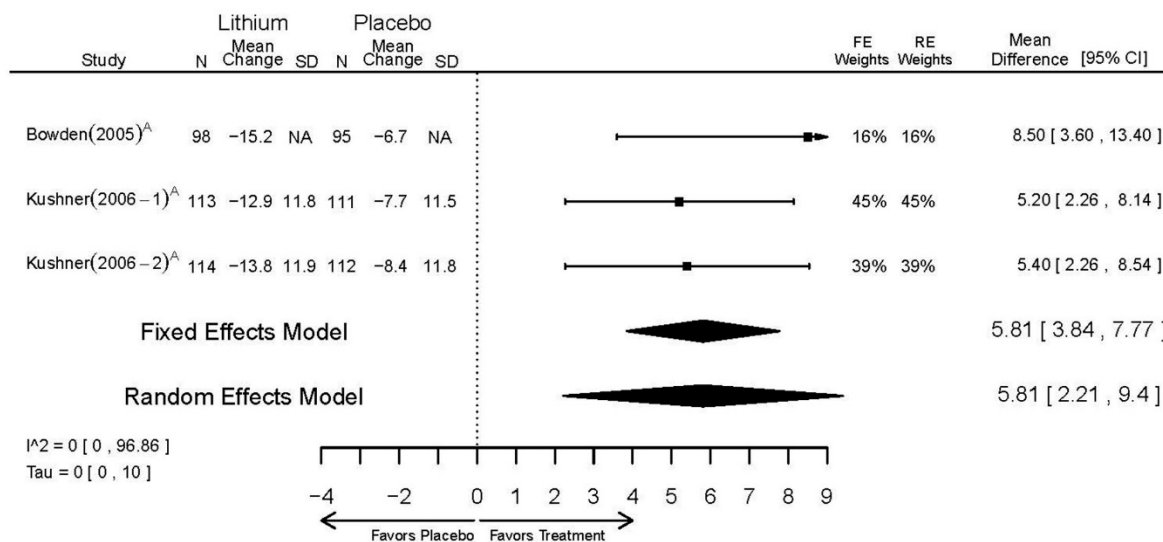
Appendix Figure F2. Lithium vs. placebo – response

Odds Ratio of Response (> 50% Reduction in YMRS) at 3 Weeks



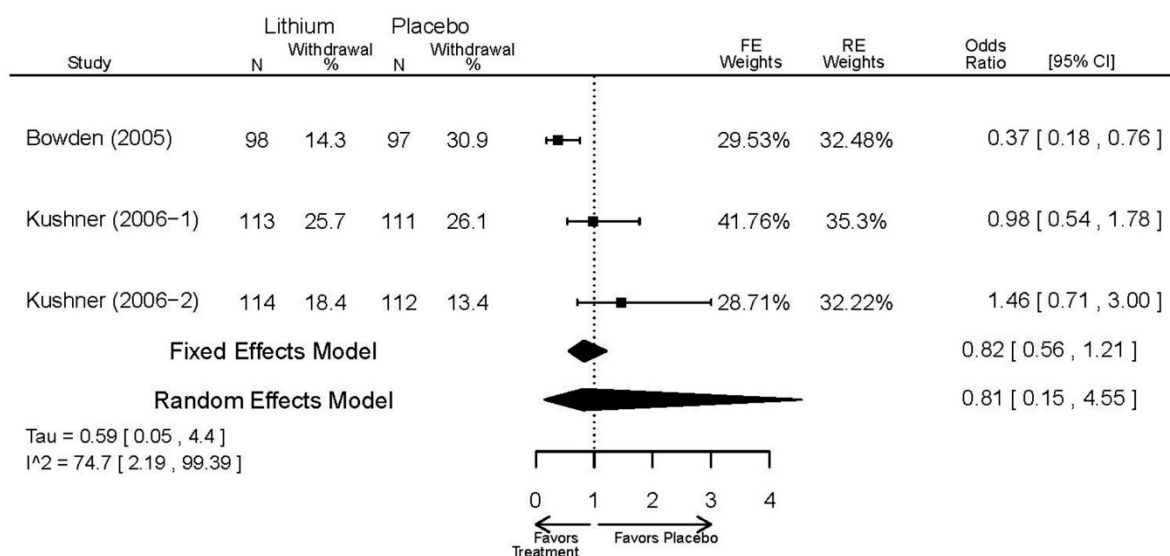
Appendix Figure F3. Lithium vs. placebo – YMRS

Difference in Mean Change in YMRS from Baseline to 3 Weeks



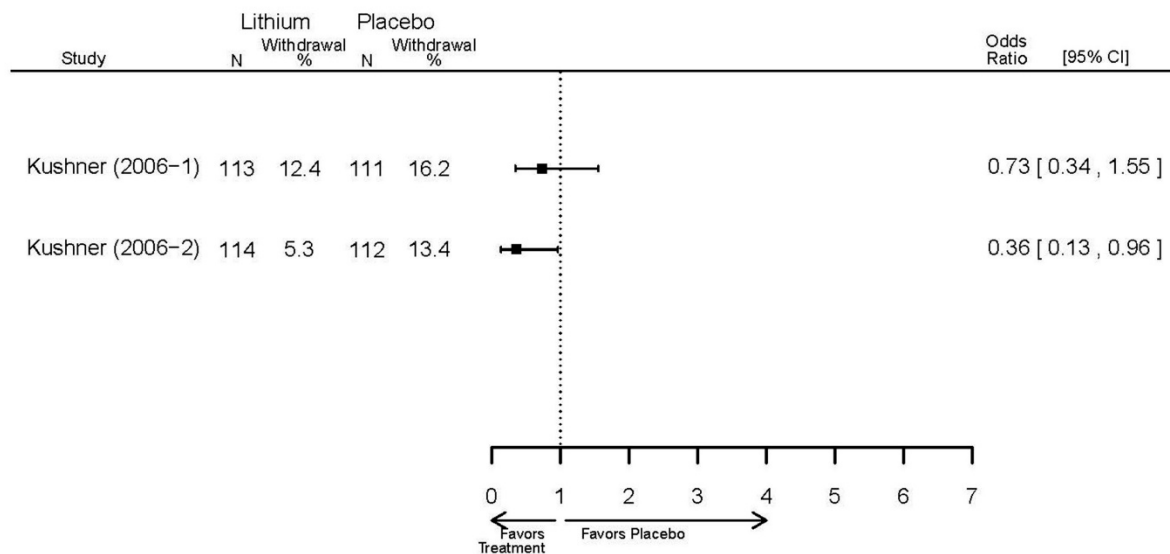
Appendix Figure F4. Lithium vs. placebo – overall withdrawal

Odds Ratio of Overall Withdrawal



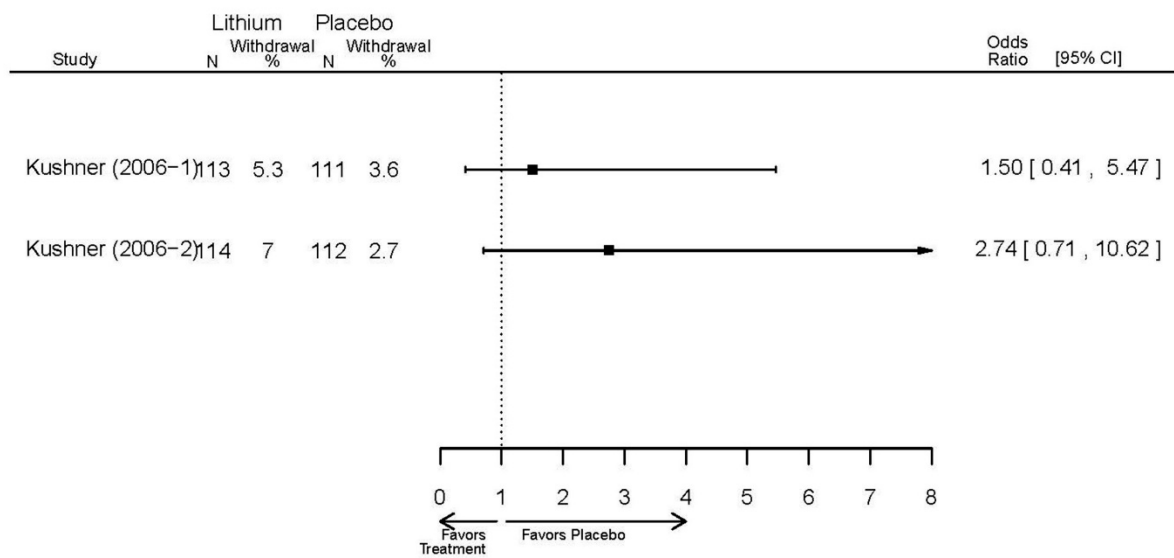
Appendix Figure F5. Lithium vs. placebo – withdrawal lack of efficacy

Odds Ratio of Withdrawal due to Lack of Efficacy at 3 Weeks



Appendix Figure F6. Lithium vs. placebo – withdrawal adverse events

Odds Ratio of Withdrawal due to Adverse Events at 3 Weeks



Appendix Table F17. Outcomes summary: lithium versus placebo for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium vs. placebo	Bowden, 2005 ¹⁰ 15669897 Moderate	<u>Response</u> See forest plot F1 above <u>Remission</u> See forest plot F2 above	<u>YMRS</u> See forest plot F3 above	<u>CGI-BP</u> 12 weeks Favors Lithium Lithium= -2.2 Placebo=-0.9 Difference in Difference (SD)= 1.3 (0.38) p<0.001	<u>Overall Withdrawal</u> See forest plot F4 above <u>Withdrawal due to Lack of Efficacy</u> 12 weeks Favors Lithium Lithium= 12/98 Placebo=38/97 OR=0.22 (95% CI 0.10, 0.45) p<0.0001 <u>Withdrawal due to AEs</u> 12 weeks NS Lithium= 6/98 Placebo=4/97 OR=1.49 (95% CI 0.40, 6.26) p=0.75	<u>EPS</u> 12 weeks Lithium= 21/98* Placebo=35/97 *May be more cases, exact number NR <u>Emergent Depression</u> 12 weeks Lithium= 8/95 Placebo=3/97 <u>Akathisia</u> 12 weeks Lithium= 3/98 Placebo=6/97
	Kushner, 2006 ⁹ 16411977 Low	<u>Response</u> See forest plot F1 above <u>Remission</u> See forest plot F2 above	<u>YMRS</u> See forest plot F3 above	NR	<u>Overall Withdrawal</u> See forest plot F4 above <u>Withdrawal Lack of Efficacy</u> See forest plot F5 above <u>Withdrawal due to AEs</u> See forest plot F6 above	<u>Severe AEs</u> 3 weeks (Placebo) 12 weeks (Lithium) Lithium= 4/227 Placebo=9/427 <u>Emergent Depression</u> 3 weeks (Placebo) 12 weeks (Lithium) Lithium= 16/227 Placebo=51/427 <u>Emergent Depression</u> 12 weeks (Lithium) 3 weeks (Placebo) 3 cases of suicidal ideation in placebo group.

Abbreviations: AE=Adverse Effects; BMI=Body Mass Index; CGI= Clinical Global Impressions; CGI-BP =Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I= Clinical Global Impressions-Improvement; CGI-S=CGI-Severity; CI= Confidence Interval; EPS=Extrapyramidal

Side Effects; GAS= Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OPT=Optimized Personalized Treatment; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE= Serious Adverse Events; SD=Standard Deviation; SE=Standard Error; YMRS = Young Mania Rating Scale

Appendix Table F18. Strength of evidence assessment: lithium versus placebo for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lithium vs. placebo	Remission 3 wks Response 3 wks	1 RCT + 1 IPD (n=325)	Favors Lithium	Moderate	Consistent	Direct	Imprecise	Low
	YMRS 3 wks	3 RCTs (n=325)	Favors Lithium MD 5.81 (95% CI 2.21, 9.4)	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – Overall 3 wks	3 RCTs (n=325)	NS	Moderate	Consistent	Direct	Imprecise	Low
	Withdrawal – Lack of Efficacy, AE	1 IPD (n=450)	NS	Moderate	Consistent	Direct	Imprecise	Low
	CGI	1 RCT (n=193)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Events; CGI= Clinical Global Impressions; CI=Confidence Interval; IPD=Individual patient data; MADRS=Montgomery-Asberg Depression Rating Scale; MD=Mean Difference; NS=Not Significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table F19. Outcomes summary: lithium active comparator for acute mania

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium vs. haloperidol	Segal, 1998 ¹¹ 9617509 Moderate	NR	<u>MRS</u> 4 weeks NS Lithium= -19.3 Haloperidol=-19.9	CGI-BP 4 weeks NS No additional data reported	<u>Overall Withdrawal</u> 4 weeks NS Lithium= 1/15 Haloperidol=3/15 p=0.06	NR
Lithium vs. valproate	Bowden, 2010 ¹² 20101186 Moderate	<u>Response</u> 12 weeks Valproate 79.5% Lithium 72.6% NS <u>Remission (YMRS/MADRS)</u> 12 weeks Valproate 71.3% Lithium 65.9% NS <u>Remission (YMRS/CGI)</u> 12 weeks Favors valproate Valproate 71.9% Lithium 58.5% p=0.025	<u>YMRS Change (90% CI)</u> 12 weeks Valproate -17.3 (9.4) Lithium -15.8 (5.3) NS	<u>CGI-BP-S Change</u> 12 weeks Valproate -2.1 (1.4) Lithium -2.3 (1.3) NS	<u>Overall Withdrawal</u> Lithium 38/135 Valproate 34/122 Withdrawal Lack of efficacy Lithium 13/135 Valproate 13/122 Withdrawal AE Lithium 9/138 Valproate 8/122	<u>Serious Adverse Events</u> 12 weeks 10 in valproate 5 in lithium Weight gain >7% Lithium 9% Valproate 7%

Abbreviations: AE=Adverse Effects; BPRS=Brief Psychiatric Rating Scale; CGI= Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-I=Clinical Global Impressions Scale-Improvement; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Syndrome Scale; MRS=mania rating scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE= Serious Adverse Events; SD=standard deviation; SDMS-D=Symptoms of Depression and Mania Scale-Depression; YMRS = Young Mania Rating Scale

Appendix Table F20. Strength of evidence assessment: lithium versus active comparator for acute mania

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lithium vs. haloperidol	YMRS CGI	1 RCT (n=30)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Lithium vs. divalproex	Response Remission YMRS CGI-BP-S Withdrawals	1 RCT (n=270)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AE=Adverse Event; CGI=Clinical Global Impressions Scale; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; n=number; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

References for Appendix F

1. Weisler RH, Hirschfeld R, Cutler AJ, et al. Extended-release carbamazepine capsules as monotherapy in bipolar disorder : pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs*. 2006;20(3):219-31. PMID: 16529527.
2. Vasudev K, Goswami U, Kohli K. Carbamazepine and valproate monotherapy: feasibility, relative safety and efficacy, and therapeutic drug monitoring in manic disorder. *Psychopharmacology*. 2000 May;150(1):15-23. PMID: 10867972.
3. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. *Arch Gen Psychiatry*. 1991 Oct;48(10):915-21. PMID: 1929761.
4. Lerer B, Moore N, Meyendorff E, et al. Carbamazepine versus lithium in mania: a double-blind study. *J Clin Psychiatry*. 1987 Mar;48(3):89-93. PMID: 3546274.
5. Tohen M, Vieta E, Goodwin GM, et al. Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study. *Journal of Clinical Psychiatry*. 2008 Nov;69(11):1776-89. PMID: 19014751.
6. Bowden CL, Swann AC, Calabrese JR, et al. A randomized, placebo-controlled, multicenter study of divalproex sodium extended release in the treatment of acute mania. *Journal of Clinical Psychiatry*. 2006 Oct;67(10):1501-10. PMID: 17107240.
7. Xu L, Lu Y, Yang Y, et al. Olanzapine-valproate combination versus olanzapine or valproate monotherapy in the treatment of bipolar imania: A randomized controlled study in a chinese population group. *Neuropsychiatric Disease and Treatment*. 2015 25 May;11:1265-71. doi: <http://dx.doi.org/10.2147/NDT.S81146>. PMID: 26060401 (pubmed) 2015078440 (embase).
8. Ichim L, Berk M, Brook S. Lamotrigine compared with lithium in mania: a double-blind randomized controlled trial. *Annals of Clinical Psychiatry*. 2000 Mar;12(1):5-10. PMID: 10798820.
9. Kushner SF, Khan A, Lane R, et al. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disorders*. 2006 Feb;8(1):15-27. PMID: 16411977.
10. Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *Journal of Clinical Psychiatry*. 2005 Jan;66(1):111-21. PMID: 15669897.
11. Segal J, Berk M, Brook S. Risperidone compared with both lithium and haloperidol in mania: a double-blind randomized controlled trial. *Clinical Neuropharmacology*. 1998 May-Jun;21(3):176-80. PMID: 9617509.
12. Bowden CL, Mosolov S, Hranov L, et al. Efficacy of valproate versus lithium in mania or mixed mania: a randomized, open 12-week trial. *International Clinical Psychopharmacology*. 2010 Mar;25(2):60-7. doi: <http://dx.doi.org/10.1097/YIC.0b013e328333ac1b> . PMID: 20101186.

Appendix G. Other Drugs for Acute Mania

Section 1. Allopurinol

Appendix Table G1. Characteristics of eligible studies: allopurinol for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Jahangard, 2014 ¹ RCT Singesite Iran Nonprofit RoB Low 24953766	N = 60 Mean Age NR Female NR Race NR BP I 100% Inpatient	Manic; YMRS ≥ 28 Schizoaffective Substance Abuse Other Mental Health Pregnant/Nursing	Allopurinol 600 mg/day + sodium valproate (15–20 mg/kg) and benzodiazepines	Placebo + sodium valproate (15–20 mg/kg) and benzodiazepines	4 weeks	YMRS Remission (YMRS ≤ 7) CGI Withdrawal 18%
Weiser, 2014 ² RCT Multisite Romania Nonprofit RoB High 24712840	N = 180 Mean Age 47 Female 66% White 100% BP I 100% Inpatient or Outpatient	Manic; Clinical Interview in DSM-IV treated with mood stabilizer or neuroleptics for between 3 days and 2 weeks. None Specified	Allopurinol 300 mg/day + mood stabilizer and/or antipsychotic	Placebo+ mood stabilizer and/or antipsychotic	6 weeks	Response (YMRS ≥ 50% improvement) YMRS CGI-BP PANSS AEs Withdrawal 17%
Fan, 2012 ³ RCT Singesite United States Nonprofit RoB Medium 22420596	N = 27 Mean Age 43 Female 50% White 63% BP I 100% Outpatient	Manic; YMRS ≥ 14 partial response to lithium, valproate, carbamazepine, or atypical antipsychotics Substance Abuse Other Mental Health Pregnant/Nursing Labs/Other Conditions	Allopurinol 600 mg/day (300 mg/day first week) Current psychiatric medications	Placebo + current psychiatric medications	6 weeks	YMRS HAM-D CGI SDS Q-LES-Q Withdrawal 15%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Machado-Vieira, 2008 ⁴ RCT Brazil Non-Profit RoB Moderate 18681754	N = 180 Mean Age 29.3 Female 59% White NR BP I 100% Not Disclosed	Manic; YMRS≥22 Schizoaffective Substance abuse Other mental health Taking other meds Labs/other conditions	T1: Allopurinol 60 mg/day T2: Dipyridamole 200 mg/day Lithium 600-900 mg/day serum level 0.6-1.2 mmol/L (mean 0.99 mmol/L)	Placebo Lithium 600-900 mg/day serum level 0.6-1.2 mmol/L (mean 0.95 mmol/L)	4 weeks	CGI-S Remission (YMRS≤7) (YMRS≤12) Response (50% improved YMRS) Adverse Events Lab Values Withdrawal 20%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trials; YMRS = Young Mania Rating Scale

Appendix Table G2. Summary risk of bias assessments: allopurinol for mania

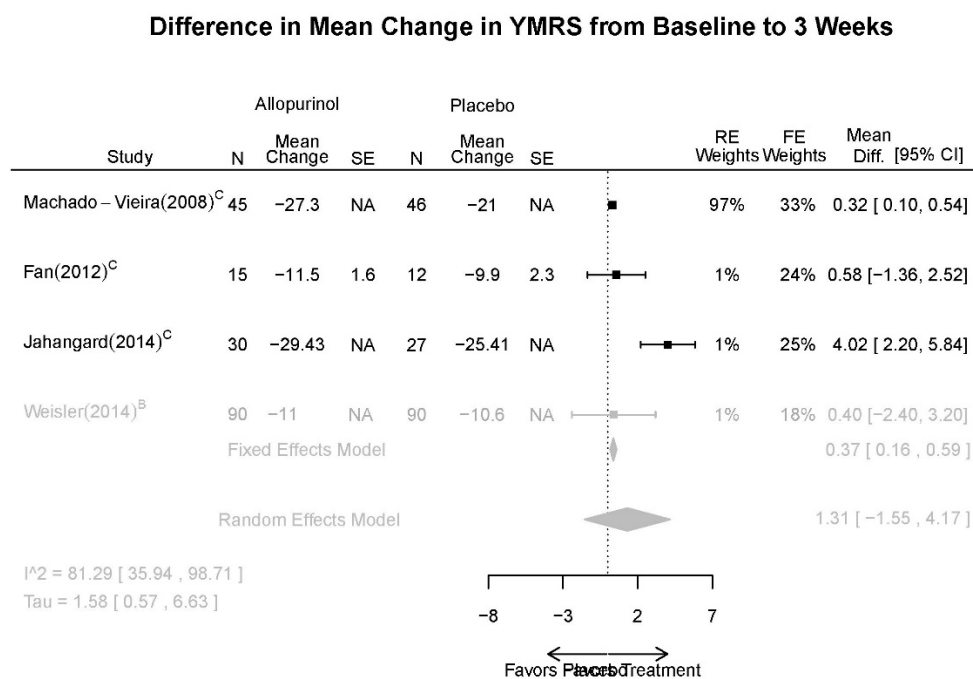
Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Allopurinol	Jahangard, 2014 ¹ No external funding 24953766	Low	No sources of bias identified.
	Weiser, 2014 ² Non-Profit 24712840	High	Randomization and blinding not described. The original study design allows for any prescribed adjunctive medication so the medication effects cannot be localized to one drug. These treatments are not measured as part of the baseline or endpoint characteristics to ensure comparison group is similar to treatment group.
	Fan, 2012 ³ Not reported 22420596	Moderate	Randomization and blinding procedures not described.
	Machado-Vieira, 2008 ⁴ Non-Profit 18681754	Moderate	22% (39/180) of patients randomized not included in results (censored due to discontinuance), unclear how this group compares to general population. Dropout rates appear similar.

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial;

Allopurinol Forest Plots

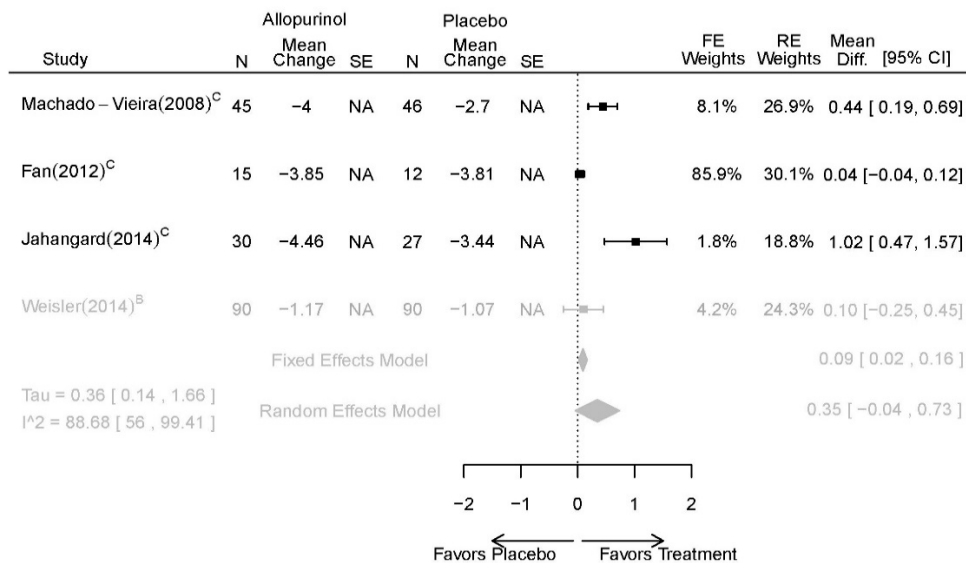
Outcomes in studies assessed as having a high risk of bias, or low to moderate risk of bias but at least 40 percent attrition, are presented in grey tones. Both fixed-effect models and random-effects models are presented. We calculated fixed-effect models to provide a charitable estimate of the average effect among completed trials. However, we base our main conclusions on the random-effects models.

Appendix Figure G1. Allopurinol vs. placebo – YMRS



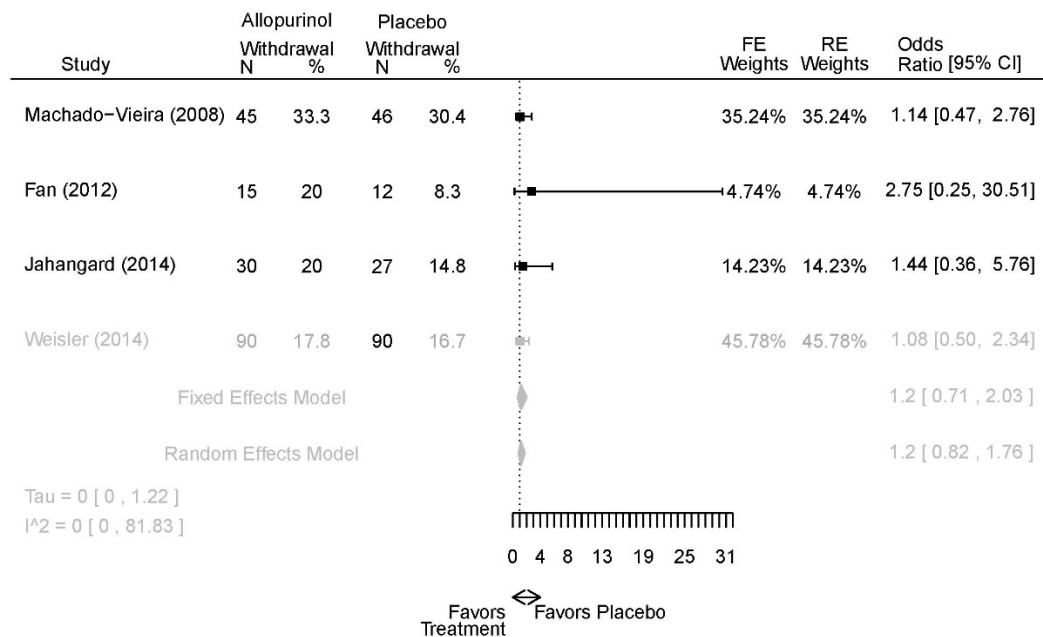
Appendix Figure G2. Allopurinol vs. placebo – CGI

Difference in Mean Change in CGI-BP-S (Overall) from Baseline to 3 Weeks



Appendix Figure G3. Allopurinol vs. placebo – overall withdrawal

Odds Ratio of Overall Withdrawal



Appendix Table G3. Outcomes summary: allopurinol for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Allopurinol + mood stabilizers vs. placebo + mood stabilizers	Jahangard, 2014 ¹ Low 24953766	<u>Remission</u> (YMRS≤7) 4 weeks Allopurinol: 24/30 Placebo: 1/27 OR: 9.46 (1.19,81.57)	<u>See forest plot G1 above</u>	<u>See forest plot G2 above</u>	<u>See forest plot G3 above</u> Withdrawal Overall: 17% Efficacy: NR AEs: NR	No reported SAE
	Weiser, 2014 ² High 24712840	<u>Response</u> (YMRS≥50% decrease) 4 weeks Allopurinol: 34/90 Placebo: 35/90 NS OR 0.95 (0.52,1.74)	<u>See forest plot G1 above</u>	<u>See forest plot G2 above</u>	<u>See forest plot G3 above</u> Withdrawal Overall: 17% Efficacy: NR AEs: NR	No reported SAE
	Fan, 2012 ³ Moderate 22420596	<u>NR</u>	<u>See forest plot G1 above</u>	<u>See forest plot G2 above</u>	<u>See forest plot G3 above</u> Withdrawal Overall: 15% Efficacy: NR AEs: NR	NR
	Machado-Vieira, 2008 ⁴ Moderate 18681754	<u>Remission</u> (YMRS≤7) 4 weeks Allopurinol: 32/45 Placebo: 15/46 OR: 5.09 (2.09,12.41) <u>Response</u> (YMRS≥50% decrease) 4 weeks Allopurinol: 36/45 Placebo: 29/56 NS 2.34 (0.91, 6.03)	<u>See forest plot G1 above</u>	<u>See forest plot G2 above</u> Linear mixed model showed drug main effect was significant (p=0.004), and mixed effects with time were significant (p≤0.001)	NR Withdrawal Overall: 22% Efficacy: 5.6% AEs: 5.56	No reported SAE

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G4. Strength of evidence assessment: allopurinol for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Allopurinol + lithium vs. placebo + lithium	Remission 4 wks	2 RCT (n=96)	See table above	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Response 4 wks	2 RCT (n=96)	See table above	High	Consistent	Direct	Imprecise	Insufficient
	YMRS 4 wks CGI 4 wks Overall Withdrawal	4 RCT (n=355)	NS	Moderate	Consistent	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table G5. Outcomes summary: allopurinol for mania vs. active control

Drug	Study Comparison PMID	Responder/ Remitter	Symptom	Function	Other	AE
Allopurinol + lithium vs. Dipyridamole + lithium	Machado-Vieira, 2008 ⁴ Moderate 18681754	<u>Remission</u> (YMRS≤7) Favors Allopurinol p=0.03 <u>Response</u> (YMRS≥50% decrease) NS	<u>YMRS</u> 4 weeks Mean change Favors Allopurinol p<0.01	<u>CGI-S</u> 4 weeks Linear mixed model Favors Allopurinol d=0.29 (0.09, 0.49)	NR <u>Overall Withdrawal</u> Allopurinol=15/60 Dipyridamole=10/60 NS <u>Withdrawal lack of effect</u> Allopurinol=3/60 Dipyridamole=5/60 NS <u>Withdrawal adverse events</u> Allopurinol=0/60 Dipyridamole=1/60 NS	SAE 1 dipyridmol patient severe skin rash

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CGI=Clinical Global Impressions; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; RR=Risk Ratio; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G6. Strength of evidence assessment: allopurinol for mania vs. active control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Allopurinol + lithium vs. Dipyridamole + lithium	Remission 4 wks Response 4 wks YMRS 4 wks CGI 4 wks Withdrawals	1 RCT (n=120)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CI=Confidence Interval; GAF=General Assessment of Functioning Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 2. Dipyridamole

Appendix Table G7. Characteristics of eligible studies: dipyridamole for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Machado-Vieira, 2008 ⁴ RCT Brazil Non-Profit RoB Moderate 18681754	N = 180 Mean Age 29.3 Female 59% White NR BP I 100% Not Disclosed	Manic; YMRS≥22 Schizoaffective Substance abuse Other mental health Taking other meds Labs/other conditions	T1: Allopurinol 60 mg/day T2: Dipyridamole 200 mg/day Lithium 600-900 mg/day serum level 0.6-1.2 mmol/L (mean 0.99 mmol/L)	Placebo Lithium 600-900 mg/day serum level 0.6-1.2 mmol/L (mean 0.95 mmol/L)	4 weeks	CGI-S Remission (YMRS≤7) (YMRS≤12) Response (50% improved YMRS) Adverse Events Lab Values Withdrawal 20%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G8. Summary risk of bias assessments: dipyridamole for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Dipyridamole	Machado-Vieira, 2008 ⁴ Non-Profit 18681754	Moderate	22% (39/180) of patients randomized not included in results (censored due to discontinuance), unclear how this group compares to general population. Dropout rates appear similar.

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table G9. Outcomes summary: dipyridamole for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Dipyridamole + lithium vs. placebo + lithium	Machado-Vieira, 2008 ⁴ Moderate 18681754	<u>Remission</u> (YMRS≤7) NR <u>Response</u> (YMRS≥50% decrease) NR	<u>YMRS</u> 4 weeks NS NR Linear mixed model showed drug main effect was not significant (p=0.11)	<u>CGI-S</u> 4 weeks NS p=0.13 Linear mixed model showed drug main effect was significant (p=0.004), and mixed effects with time were significant (p≤0.001)	NR <u>Overall Withdrawal</u> Dipyridamole=10/60 Placebo=14/60 NS <u>Withdrawal lack of efficacy</u> Dipyridamole=5/60 Placebo=7/60 NS <u>Withdrawal adverse events</u> Dipyridamole=1/60 Placebo=0/60 NS	1 dipyridamole participant with severe adverse event skin rash

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G10. Strength of evidence assessment: dipyridamole for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Dipyridamole + lithium vs. placebo + lithium	YMRS 4 wks CGI-S 4 wks Withdrawals	1 RCT (n=120)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 3. Celecoxib

Appendix Table G11. Characteristics of eligible studies: celecoxib for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Arabzadeh, 2015 ⁵ RCT Iran University RoB Low 26291962	N = 48 Mean Age 31.4 Female 35% White NR BP I 100% Inpatient	Manic; YMRS≥20 Schizoaffective Substance abuse Other mental health Taking other meds Labs/other conditions	Celecoxib 400 mg/day	Placebo	6 weeks	YMRS HAM-D Remission (YMRS≤7) Time to Remission Response (YMRS≥50% decrease) Adverse Events Withdrawal 4%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G12. Summary risk of bias assessments: celecoxib for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Celecoxib	Arabzadeh, 2015 ⁵ University 26291962	Low	No sources of bias identified

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial;

Appendix Table G13. Outcomes summary: celecoxib for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Celecoxib vs. placebo	Arabzadeh, 2015 ⁵ Low 26291962	<u>Response</u> (YMRS \geq 50% decrease) 3 weeks NS (p=0.08) 6 weeks NS p=0.11 <u>Remission</u> (YMRS \leq 7) 3 weeks NS p=0.15 6 weeks Favors celecoxib p=0.002	<u>YMRS</u> 3 weeks Favors celecoxib Mean difference -5.17 (-9.61, -0.74) p=0.006 6 weeks Favors celecoxib p<0.001	NR	NR <u>Withdrawal</u> Celecoxib=1/24 Placebo=1/24 NS	<u>Serious Adverse Events</u> 6 weeks 0 in both arms <u>Deaths</u> 6 weeks 0 in both arms <u>EPS</u> NR

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G14. Strength of evidence assessment: celecoxib for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Celecoxib vs. placebo	Remission 3 wks Response 3 wks YMRS 3 wks Withdrawals	1 RCT (n=44)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 4. Donepezil

Appendix Table G15. Characteristics of eligible studies: donepezil for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Chen, 2013 ⁶ RCT China Non-profit RoB Moderate 23807849	N = 30 Mean Age 34.1 Female 40% White (%) NR BP I 100% Inpatient	Manic; YMRS>20 Schizoaffective Substance abuse Other mental health Taking other meds Pregnant/nursing Labs/other conditions	Donepezil 10 mg/day Lithium 600-900 mg/day serum level 0.8-1.2 mmol/L (mean 0.83 mmol/L)	Placebo Lithium 600-900 mg/day serum level 0.8-1.2 mmol/L (mean 0.82 mmol/L)	4 weeks	BPRS YMRS Response (YMRS decrease ≥50%) Remission (YMRS≤12) Adverse Events Withdrawal 0%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G16. Summary risk of bias assessments: donepezil for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Donepezil	Chen, 2013 ⁶ Nonprofit 23807849	Moderate	Randomization and blinding procedures not described.

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table G17. Outcomes summary: donepezil for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Donepezil + lithium vs. placebo + lithium	Chen, 2013 ⁶ Moderate 23807849	<u>Remission</u> (YMRS _≤ 12) 4 weeks NS p=0.27 <u>Response</u> (YMRS _≥ 50% decrease) 4 weeks NS p=1.0	<u>YMRS Decrease</u> 4 weeks NS p=0.16	NR	No withdrawals	Reported no serious adverse events

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G18. Strength of evidence assessment: donepezil for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Donepezil + lithium vs. placebo + lithium	Response 4 wks Remission 4 wks YMRS 4 wks	1 RCT (n=30)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 5. Endoxifen

Appendix Table G19. Characteristics of eligible studies: endoxifen for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Ahmad, 2016 ⁸ RCT India Industry ROB Low 27346789	N=66 Mean Age 33 Female 52% Race NR BP I 100% Inpatient	Manic/Mixed; YMRS ≥ 20 and CGI-S ≥ 4 New diagnosis Labs/other conditions Pregnant/nursing	Endoxifen oral enteric coated tablets at two fixed doses T1: 4 mg/day T2: 8 mg/day)	Divalproex 1000 mg/day	3 weeks	Response (YMRS decrease $\geq 50\%$) CGI-S YMRS MADRS Withdrawal 7%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trials; YMRS = Young Mania Rating Scale

Appendix Table G20. Summary risk of bias assessments: endoxifen for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Endoxifen	Ahmad, 2016 ⁸ Industry 27346789	Low	Well-disclosed and reported study.

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial;

Appendix Table G21. Outcomes summary table: endoxifen for mania vs. active control

Drug	Study Comparison PMID	Responder/ Remitter	Symptom	Function	Other	AE
Endoxifen vs. divalproex	Ahmad, 2016 ⁸ Low 27346789	<u>Response</u> (YMRS≥50% decrease) 3 weeks NS Endoxifen 4 mg: 44% Endoxifen 8 mg: 64% Divalproex:: 72%	<u>YMRS</u> 3 weeks NS Mean change Endoxifen 4 mg: -12.65 Endoxifen 8 mg: -16.21 Divalproex:: -16.38	<u>CGI-S</u> 3 week Reported NS (details not reported)	2 patients withdrew due to adverse events 4 mg arm	<u>Serious Adverse Events</u> 3 weeks 2 4 mg arm (delusions) No deaths

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CGI=Clinical Global Impressions; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; RR=Risk Ratio; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G22. Strength of evidence assessment: endoxifen for mania vs. active control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Endoxifen vs. divalproex	Remission 3 wks YMRS 3 weeks CGI-S 3 weeks	1 RCT (4 mg: n=42 (8 mg: n=42)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CI=Confidence Interval; GAF=General Assessment of Functioning Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 6. Gabapentin

Appendix Table G23. Characteristics of eligible studies: gabapentin for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Astaneh, 2012 ⁷ RCT Single-site Iran University RoB High 22978083	N = 60 Mean Age NR Female about 50% White NR BP I NR Inpatient	Mania; Not Defined Substance abuse	Gabapentin 900 mg/day Lithium NR	Placebo Lithium NR	6 week	YMRS Withdrawal 0

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G24. Summary risk of bias assessments: gabapentin for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Gabapentin	Astaneh, 2012 ⁷ University 22978083	High	Clinical and demographic traits at baseline not reported or compared for similarity. Blinding of staff and patients not addressed. Reporting is insufficient and may be misleading (e.g. missing values in graphs, missing error bars in graphs, raw data not provided/only sum of squares, asserts statistically meaningful improvement when improvement not shown statistically).

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table G25. Outcomes summary: gabapentin for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Gabapentin + lithium vs. placebo + lithium	Astaneh, 2012 ⁷ High 22978083	NR	<u>YMRS</u> Reported favors gabapentin. However, baseline YMRS gabapentin = ~50 while control = ~13.	NR	NR	NR

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G26. Strength of evidence assessment: gabapentin for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Gabapentin + lithium vs. placebo + lithium	YMRS 6 wks	1 RCT (n=60)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 7. Paliperidone

Appendix Table G27. Characteristics of eligible studies: paliperidone for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Berwaerts, 2012a ⁹ RCT 3 Continents Industry ROB Moderate 20624657	N = 469 Mean Age 40 Female 47% White 50% BP I 100% Inpatient (at least 1 week) Outpatient (weeks 2-3)	Manic/Mixed; YMRS ≥ 20 with 1 manic or mixed episode in past three years Schizoaffective; Substance abuse; Other Mental Health Condition; Taking other medications; Pregnant/Nursing	Paliperidone extended release (separate 3,6,12 mg/day arms)	Placebo	3 weeks	CGI-BP-S GAF MADRS PANSS Scale for Suicide Ideation (SSI) YMRS SAE EPS Withdrawal 39%
Berwaerts, 2011 ¹⁰ RCT 3 Continents Industry ROB Moderate 20947174	n = 300 Mean Age 40 Female 46% White 77% BP I 100% Inpatient (at least 1 week) Outpatient (weeks 2-7)	Manic/Mixed; YMRS ≥ 20 First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health Conditions; Neurological Disorders; Taking other medications; Pregnant/Nursing	Paliperidone extended release 3-12 mg/day (mean 8.1 mg/day) Lithium 0.6-1.2 mEq/L (mean NR) Or Valproate 50-125 mcg/mL (mean NR)	Placebo NA Lithium 0.6-1.2 mEq/L (mean NR) Or Valproate 50-125 mcg/mL (mean NR)	7 weeks	CGI-BP-S GAF PANSS YMRS Response (YMRS decrease $\geq 50\%$) Remission (YMRS ≤ 12) MADRS Adverse Events Withdrawal 37%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Vieta, 2010 ¹¹ RCT 3 weeks Multisite 4 Continents Industry RoB Moderate 20565430	N = 493 Mean Age 39 Female 42% White 68% BP I 100% Inpatient (at least 1 week) Outpatient (weeks 2-3)	Manic/Mixed; YMRS≥20; At least one episode within three years prior First Manic Episode Schizoaffective Substance abuse Other mental health Neurological disorders Labs/other conditions	Paliperidone extended release 3-12 mg/day (median/mode dosage 9 mg)	C1: Placebo C2: Quetiapine 400-800 mg/day	3 week (12 week excluded for attrition)	YMRS GAF PANSS CGI-BP-S Response (YMRS decrease ≥50%) Remission (YMRS≤12) Withdrawal 21% at 3 weeks
Berwaerts, 2012 ¹² RCT Multisite 5 Continents Industry RoB Moderate 22377512	N = 766 Mean Age 40 Female 52% White 62% BP I 100% Outpatient	Manic/Mixed; YMRS≥20; 2 previous mood episodes (1 of which manic/mixed) within past 3 years; First manic episode; Schizoaffective; Other mental health; Neurological disorders; Taking other meds; Pregnant/nursing; Labs/Other conditions	Paliperidone extended release 3-12 mg/day	Olanzapine 5-20 mg/day	15 weeks	Response (≥50% reduction in YMRS) Remission (YMRS and MADRS≤12) Withdrawal 49%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G28. Summary risk of bias assessments: paliperidone for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Paliperidone extended release	Berwaerts, 2012 ¹² Industry 22377512	High	Very large dropout rate among all study arms, across all time periods
	Berwaerts, 2012a ⁹ Industry 20624657	Moderate	Large dropout rate among all study arms; attrition 39%
	Vieta, 2010 ¹¹ Industry 20565430	Moderate (3 week only)	Moderate dropout rate among all study arms, across all time periods; raters may not be blinded
	Berwaerts, 2011 ¹⁰ Industry 20947174	Moderate	Large dropout rate among all study arms; attrition 37%

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table G29. Outcomes summary: paliperidone for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Paliperidone vs. placebo	Vieta, 2010 ¹¹ Moderate 20565430	<u>Responders</u> (YMRS decrease ≥50%) 3 weeks Favors Paliperidone Paliperidone=106/190 Placebo=36/104 p<0.001 <u>Remission</u> (YMRS≤12) 3 weeks Favors Paliperidone Paliperidone=99/190 Placebo=30/104 p<0.001	<u>YMRS Change</u> 3 weeks Favors treatment Least square mean difference between groups -5.5 (95% CI -7.57, -3.35) p<0.001	<u>CGI-BP-S</u> 3 week Paliperidone - 2.0 (95%CI -4, 2) Placebo -0.5 (95%CI -4, 2) Favors Paliperidone p<0.001 <u>GAF</u> 3 weeks Favors treatment Mean difference treatment: 11.6 Placebo: 12.2 p<0.001	<u>Overall Withdrawal</u> Paliperidone=40/195 Placebo=41/105 Favors Paliperidone <u>Withdrawal lack of effect</u> Paliperidone=6/195 Placebo=19/105 Favors Paliperidone <u>Withdrawal adverse events</u> Paliperidone=9/195 Placebo=5/105 NS	<u>Serious AE</u> NR <u>EPS</u> No serious events in any treatment arm

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
	Berwaerts, 2012a ⁹ Moderate 20624657	<u>Responders</u> (YMRS decrease ≥50%) 3 weeks NS <u>Remission</u> (YMRS≤12) 3 weeks NS	<u>YRMS Change</u> 3 weeks Least square mean difference Paliperidone 12 mg: - 13.5 (9.17) n=109 Placebo: -10.1 (10.21) Difference between groups 3.4 n=115 p=0.025 Favors Paliperidone 12 mg (dose dependent)	<u>CGI-BP-S</u> 3 week NS <u>GAF</u> 3 weeks NS	<u>Overall Withdrawal</u> Paliperidone=132/347 Placebo=50/122 NS <u>Withdrawal lack of effect</u> Paliperidone=31/347 Placebo=24/122 Favors Paliperidone <u>Withdrawal adverse events</u> Paliperidone=25/347 Placebo=6/122 NS	<u>Serious AE</u> 1 death Paliperidone 6 mg (deemed not related) <u>EPS</u> Statistically significantly more in 12 mg paliperidone for akathisia and dystonia <u>Treatment emergent depression:</u> NS <u>>7% weight gain</u> NS
Paliperidone + mood stabilizers vs. placebo + mood stabilizers	Berwaerts, 2011 ¹⁰ Moderate 20947174	<u>Remission</u> (YMRS≤12) 6 weeks NS Paliperidone 60% Placebo 57% p=0.12 <u>Response</u> (YMRS≥50% decrease) 6 weeks NS Paliperidone 62% Placebo 56% p=0.24	<u>YMRS</u> 6 weeks Least squares mean difference NS p=0.16	<u>CGI-BP-S</u> 6 weeks NS p=0.26 <u>GAF</u> 6 weeks NS p=0.71	<u>Suicide Ideation</u> 1 in each group <u>Overall Withdrawal</u> Paliperidone=60/150 Placebo=51/150 NS <u>Withdrawal lack of effect</u> Paliperidone=12/150 Placebo=18/150 NS <u>Withdrawal adverse events</u> Paliperidone=12/150 Placebo=2/150 Favors Placebo	<u>SAE</u> 7 in each group; psychiatric disorders most common Treatment emergent depression: 1% in each group Akathisia 8% vs. 1% Favored placebo. Weight increase≥7%: Paliperidone 15% Placebo 5%

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not

significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G30. Strength of evidence assessment: paliperidone for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Paliperidone vs. placebo	Remission 3 wks Response 3 wks CGI Withdrawal – overall	2 RCT (n=763)	See table above	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Withdrawal – adverse events	2 RCT (n=763)	NS	Moderate	Consistent	Direct	Imprecise	Low
	YMRS 3 wks Withdrawal lack of efficacy	2 RCT (n=763)	Favors Paliperidone possible dose response: NS at 3 and 6 mg, benefit at 12 mg or median dosage of 9 mg	Moderate	Consistent	Direct	Imprecise	Low
Paliperidone + mood stabilizers vs. placebo + mood stabilizers	Remission 6 wks Response 6 wks YMRS 6 wks CGI-S 6 wks Withdrawals	1 RCT (n=299)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table G31. Outcomes summary: paliperidone for mania vs. active control

Drug	Study Comparison PMID	Responder/ Remitter	Symptom	Function	Other	AE
Paliperidone extended release vs. olanzapine	Berwaerts, 2012 ¹² Moderate 22377512	<u>Response</u> (YMRS decrease $\geq 50\%$) 15 weeks NS >70% responded overall <u>Remission</u> (YMRS ≤ 12) 15 weeks NS >60% achieved remission	<u>YMRS</u> Least square mean difference 15 weeks NS -0.3 (-2.12, 1.57)	<u>NR</u>	<u>Overall Withdrawal</u> 15 weeks Paliperidone: 09/617 Olanzapine: 63/149 NS <u>Withdrawal lack of effect</u> Paliperidone:30/617 Olanzapine:5/149 NS <u>Withdrawal adverse events</u> Paliperidone:63/617 Olanzapine:13/149 NS	SAE Paliperidone: 42/614 Olanzapine: 10/148 NS
Paliperidone extended release vs. quetiapine	Vieta, 2010 ¹¹ Moderate 20565430	<u>Response</u> (YMRS decrease $\geq 50\%$) 3 week Paliperidone 55.8% Quetiapine 49% NS RR 1.1 (95% CI 0.94, 1.38) <u>Remission</u> (YMRS ≤ 12) 3 week Paliperidone 52.1% Quetiapine 47.4% NS RR 1.1 (95% CI 0.90, 1.35)	<u>YMRS Change</u> 3 week LSM difference (Quet-Pali) 1.5 (95% CI -0.28, 3.22) NS p=0.099	<u>GAF Change¹</u> 3 week Paliperidone 12.2 (sd 11.17) Quetiapine 11.6 (sd 11.96) NS p=NR <u>CGI-BP-S</u> 3 week Paliperidone -2.0 (95%CI -4, 2) Quetiapine -1.0 (95%CI -4, 2) NS p=NR	<u>Switching</u> 3 week Paliperidone 4.3% Quetiapine 2.7% NS p=NR <u>Overall Withdrawal</u> Paliperidone=40/195 Quetiapine=41/193 NS <u>Withdrawal lack of effect</u> Paliperidone=6/195 Quetiapine=15/105 Favors Paliperidone <u>Withdrawal adverse events</u> Paliperidone=9/195 Quetiapine=4/193 NS	SAE NR <u>EPS</u> No serious events in any treatment arm

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CGI=Clinical Global Impressions; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; RR=Risk Ratio; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G32. Strength of evidence assessment: paliperidone for mania vs. active control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Paliperidone extended release vs. olanzapine	Remission 15 wks Response 15 wks YMRS 15 wks Withdrawals	1 RCT (n=766)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Paliperidone extended release vs. quetiapine	Remission 3 wks Response 3 wks YMRS 3 wks CGI 3 wks GAF 3 wks Withdrawals	1 RCT (n=388)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CI=Confidence Interval; GAF=General Assessment of Functioning Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 8. Tamoxifen

Appendix Table G33. Characteristics of eligible studies: tamoxifen for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Yildiz, 2008 ¹³ RCT Single-site Turkey Non-Profit RoB Moderate 18316672	N = 66 Mean Age 33 Female 52% Race NR BP I 100% Outpatient	Mania; YMRS≥20 Schizoaffective Substance abuse Other mental health Neurological disorders Taking other meds Pregnant/nursing	Tamoxifen 20-80 mg/twice daily	Placebo	3 week	CGI-BP-S HAM-D MADRS PANSS YMRS Response (YMRS decrease ≥50%) Withdrawal 24%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G34. Summary risk of bias assessments: tamoxifen for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Tamoxifen	Yildiz, 2008 ¹³ Non-Profit 18316672	Moderate	Blinding of patients, staff, raters not described ; minor differences at baseline regarding pretreatment drugs may create residual confounding

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial;

Appendix Table G35. Outcomes summary: tamoxifen for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Tamoxifen vs. placebo	Yildiz, 2008 ¹³ Moderate 18316672	<u>Response</u> (YMRS decrease ≥50%) 3 weeks Favors tamoxifen Tamoxifen=14/29 Placebo=1/21 p=0.003 <u>Remission</u> (YMRS≤12) 3 weeks Favors tamoxifen Tamoxifen=8/29 Placebo=0/21 p=0.03	<u>YMRS Decrease Rate</u> Over 3 weeks Favors tamoxifen Linear mixed model p<0.001 <u>YMRS (Mean SD)</u> Week 0 Tamoxifen 38.6 (5.0) Placebo 37.2 (6.6) Week 3 Tamoxifen 20.3 (11.2) Placebo 40.1 (10.4)	NR	NR <u>Withdrawal</u> Tamoxifen=6/35 Placebo=10/31 NS	<u>Serious Adverse Events</u> 1 Tamoxifen – Suicide Attempt 1 Placebo – Suicide Attempt

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G36. Strength of evidence assessment: tamoxifen for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Tamoxifen vs. placebo	Remission 3 wks Response 3 wks YMRS 3 wks Withdrawals	1 RCT (n=50)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 9. Topiramate

Appendix Table G37. Characteristics of eligible studies: topiramate for acute mania

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Bahk, 2005 ¹⁴ Open-label RCT Multisite South Korea Industry ROB High 15610953	N=74 Mean Age 37 Female 51% Race Asian BP-I 100% Outpatient	Mania YMRS≥20 Other mental health Pregnant/nursing Labs/other conditions Taking other meds	Topiramate average 220.6 mg/day + Risperidone average 3.4 mg/day	Divalproex average 908.3 mg/day Risperidone average 3.3 mg/day	3 week	YMRS CGI Adverse Events Withdrawal 18%
Chengappa, 2006 ¹⁵ RCT Multisite US Low Industry RoB Low 17196048	N = 287 Mean Age 40 Female 56% White 84% BP I 100% Outpatient	Manic/Mixed; YMRS≥18 Received lithium or valproate at least 6 weeks, including stable dose 2 weeks prior to screening within specified serum levels Substance abuse Other mental health Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions	T1: Topiramate 50-400mg/day (mean 6.2 mcg/mL day 42, 7.8 mcg/mL day 84) Lithium mean 0.7 mEq/L Valproate mean 69.8 mcg/mL	Placebo Lithium mean 0.7 mEq/L Valproate mean 71.0 mcg/mL	12 week	YMRS CGI-S BPRS MADRS GAS Weight Response (≥50% improvement in YRMS) Withdrawal 38%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kushner, 2006 ¹⁶ Pooled Analysis of 4 RCTs (3 week data) Multisite 6 Continents Industry RoB Low 16411977	N = 876 (includes only 400 mg/day topiramate arms and placebo arms Mean Age 41 Female 51% White 75% BP I 100% Inpatient (at least 4 days, as clinically warranted)	Manic/Mixed; YMRS≥20 First Manic Episode Schizoaffective Substance abuse Other mental health Taking other meds Pregnant/nursing Labs/other conditions	Topiramate 400mg/day (mean 313mg/day) (only 400 mg/day arms were common across pooled studies)	C1: Placebo C2: Lithium 300-1800 mg/day (0.8-1.2mEq/L)	3 week	Weight YMRS Withdrawal 27%

Abbreviations: AE=Adverse Effects; BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impressions; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; EPS=Extrapyramidal Symptoms; GAF=General Assessment of Functioning Scale; GAS= Global Assessment Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR= not reported; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; PANSS=Positive and Negative Syndrome Scale; PMID=PubMed Identification Number; RCT= Randomized Controlled Trial; RoB=risk of bias; SAE=Serious Adverse Events; SDS=Sheehan Disability Scale; T=Trial; YMRS = Young Mania Rating Scale

Appendix Table G38. Summary risk of bias assessments: topiramate for mania

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Topiramate	Bahk, 2005 ¹⁴ Industry 15610953	High	Randomization and allocation concealment not specified, open label dosing
	Kushner, 2006 ¹⁶ Industry 16411977	Low	Well-disclosed and reported study (RCTs unique to this publication.)
	Chengappa, 2006 ¹⁵ Industry 17196048	Low	Well-disclosed and reported study

Abbreviations: PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table G39. Outcomes summary: topiramate for mania vs. inactive control

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Topiramate vs. placebo	Kushner, 2006 ¹⁶ Low 16411977	NR	<u>YMRS Change</u> 3 weeks NS Mean difference (top-plac) 0.60 (95% CI -0.85, 2.0) p=0.418 n=434 I, n=317 C	NR	<u>Overall Withdrawal</u> Topiramate=123/331 Placebo=85/317 Favors Placebo <u>Withdrawal lack of effect</u> Topiramate=52/331 Placebo=39/317 NS <u>Withdrawal adverse events</u> Topiramate=20/331 Placebo=9/317 Favors Placebo	<u>SAE</u> Topiramate 3% Placebo 2% <u>Suicide Attempt</u> 3 weeks Topiramate 2/656 Placebo 0/429 (reported over 4 pooled RCTs, not 3 monotherapy tests)

Comparison	Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Topiramate+mood stabilizer vs. placebo+mood stabilizer	Chengappa, 2006 ¹⁵ Low 17196048	<u>Response</u> (YMRS≥50% decrease) 12 weeks NS Topiramate 39% Placebo 38% p=0.914	<u>YMRS Change</u> 12 weeks NS Topiramate -10.1±8.7 Placebo -9.6±8.2 p=0.797	<u>CGI-S Change</u> 12 weeks NS Topiramate -0.9±1.1 Placebo -0.9±1.1 p=0.698 <u>GAS Change</u> 12 weeks NS Topiramate 7.2±9.9 Placebo 7.1±11.5 p=0.838	<u>BMI Change</u> 12 weeks Favors Topiramate Topiramate -0.84±1.2 kg/m ² Placebo 0.07±1.1 kg/m ² p<0.001 <u>Suicide Ideation</u> Topiramate 1 patient Placebo 2 patients <u>Overall Withdrawal</u> Topiramate=57/143 Placebo=53/144 NS <u>Withdrawal lack of effect</u> Topiramate=6/143 Placebo=4/144 NS <u>Withdrawal adverse events</u> Topiramate=20/143 Placebo=10/144 Favors Placebo	NR

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CI=Confidence Interval; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S= Clinical Global Impressions, Severity Scale; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; RCT=randomized controlled trial; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G40. Strength of evidence assessment: topiramate for mania vs. inactive control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Topiramate vs. placebo	YMRS 3 wks Withdrawal – lack of effect	4 RCT (1 IPD) (n=876)	NS	Low	Consistent	Direct	Imprecise	Low
	Withdrawals – overall	4 RCT (1 IPD) (n=876)	Favors Placebo 37.2% vs. 26.8%, p=0.005	Low	Consistent	Direct	Imprecise	Low
	Withdrawals – adverse events	4 RCT (1 IPD) (n=876)	Favors Placebo 6.04% vs. 2.84%, p=0.049	Low	Consistent	Direct	Imprecise	Low
Topiramate +mood stabilizer vs. placebo+moo d stabilizer	Response 12 wks YMRS 12 wks CGI-S 12 wks Withdrawals	1 RCT (n=287)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CGI-S=Clinical Global Impressions, Severity Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table G41. Outcomes summary: topiramate for mania vs. active control

Drug	Study Comparison PMID	Responder/ Remitter	Symptom	Function	Other	AE
Topiramate vs. lithium	Kushner, 2006 ¹⁶ Low 16411977	NR	<u>YMRS Change</u> 3 week Mean difference (top-lith) 6.14 (95% CI 3.94, 8.34) Favors Lithium p<0.001	NR	<u>Weight</u> 3 week Mean difference (top-lith) -1.82% (95% CI -2.90%, -0.74%) Favors Topiramate p<0.001 <u>Overall Withdrawal</u> Topiramate=47/226 Lithium=51/227 NS <u>Withdrawal lack of effect</u> Topiramate=23/226 Lithium=19/227 NS <u>Withdrawal adverse events</u> Topiramate=6/226 Lithium=17/227 Favors Topiramate p=.019	<u>SAE</u> Topiramate 3% Lithium 1.5%
Topiramate + risperidone vs. divalproex + risperidone	Bahk, 2005 ¹⁴ High 15610953	<u>Response</u> (YMRS decrease ≥50%) 15 weeks NS >70% responded overall <u>Remission</u> (YMRS≤12) 15 weeks NS >60% achieved remission	<u>YMRS</u> 6 weeks NS (Both groups improved statistically significantly)	<u>CGI</u> 6 weeks NS (Both groups improved statistically significantly)	<u>BMI</u> Divalproex 73% patients increase Topiramate 25% patients decreased <u>Overall Withdrawal</u> NS Withdrawals reasons not reported by group	Reported no SAEs <u>EPS</u> NS between groups (“about 1/3 of patients in both groups”)

Abbreviations: AE=Adverse Events; BMI=Body Mass Index; CGI=Clinical Global Impressions; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; RR=Risk Ratio; SAE=Serious Adverse Events; SD=standard deviation; YMRS = Young Mania Rating Scale

Appendix Table G42. Strength of evidence assessment: topiramate for mania vs. active control

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Topiramate vs. Lithium	YMRS 3 wks	2 RCTs (1 IPD) (n=453)	Favors Lithium Mean difference 6.14 (95% CI 3.94, 8.34)	Low	Consistent	Direct	Imprecise	Low
	Withdraw – overall, lack of effect	2 RCTs (1 IPD) (n=453)	NS	Low	Consistent	Direct	Imprecise	Low
	Withdraw – adverse events	2 RCTs (1 IPD) (n=453)	Favors Topiramate 2.65% vs. 7.49%, p=0.019	Low	Consistent	Direct	Imprecise	Low
Topiramate + risperidone vs. divalproex + risperidone	Remission 6 wks Response 6 wks YMRS 6 wks CGI 6 wks Withdrawals	1 RCT (n=74)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; CI=Confidence Interval; GAF=General Assessment of Functioning Scale; IPD=Individual Patient Data; NS=not significant; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

References for Appendix G

1. Jahangard L, Soroush S, Haghighi M, et al. In a double-blind, randomized and placebo-controlled trial, adjuvant allopurinol improved symptoms of mania in in-patients suffering from bipolar disorder. *European Neuropsychopharmacology*. Jun. 2014 2, 2014(Pagination)doi: <http://dx.doi.org/10.1016/j.euroneuro.2014.05.013> . PMID: 24953766.
2. Weiser M, Burshtein S, Gershon AA, et al. Allopurinol for mania: A randomized trial of allopurinol versus placebo as add-on treatment to mood stabilizers and/or antipsychotic agents in manic patients with bipolar disorder. *Bipolar Disorders*. 2014 2014;16(4):441-7. doi: <http://dx.doi.org/10.1111/bdi.12202>. PMID: 24712840.
3. Fan A, Berg A, Bresee C, et al. Allopurinol augmentation in the outpatient treatment of bipolar mania: a pilot study. *Bipolar Disorders*. 2012 Mar;14(2):206-10. doi: <http://dx.doi.org/10.1111/j.1399-5618.2012.01001.x>. PMID: 22420596.
4. Machado-Vieira R, Soares JC, Lara DR, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. *Journal of Clinical Psychiatry*. 2008 Aug;69(8):1237-45. PMID: 18681754.
5. Arabzadeh S, Ameli N, Zeinoddini A, et al. Celecoxib adjunctive therapy for acute bipolar mania: A randomized, double-blind, placebo-controlled trial. *Bipolar Disorders*. 2015 01 Sep;17(6):606-14. doi: <http://dx.doi.org/10.1111/bdi.12324>. PMID: 26291962 (pubmed) 2015329826 (embase).
6. Chen J, Lu Z, Zhang M, et al. A randomized, 4-week double-blind placebo control study on the efficacy of donepezil augmentation of lithium for treatment of acute mania. *Neuropsychiatric Disease and Treatment*. 2013 17, 2013;9:839-45. PMID: 23807849.
7. Astaneh AN, Rezaei O. Adjunctive treatment with gabapentin in bipolar patients during acute mania. *International Journal of Psychiatry in Medicine*. 2012;43(3):261-71. PMID: 22978083.
8. Ahmad A, Sheikh S, Shah T, et al. Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen. *Clinical and Translational Science*. 2016 01 Oct;9(5):252-9. doi: <http://dx.doi.org/10.1111/cts.12407>. PMID: 27346789 PMID/611114504 Embase.
9. Berwaerts J, Xu H, Nuamah I, et al. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *Journal of Affective Disorders*. 2012 Jan;136(1-2):e51-60. doi: <http://dx.doi.org/10.1016/j.jad.2010.06.030>. PMID: 20624657.
10. Berwaerts J, Lane R, Nuamah IF, et al. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *Journal of Affective Disorders*. 2011 Mar;129(1-3):252-60. doi: <http://dx.doi.org/10.1016/j.jad.2010.09.011>. PMID: 20947174.
11. Vieta E, Nuamah IF, Lim P, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disorders*. 2010 May;12(3):230-43. doi: <http://dx.doi.org/10.1111/j.1399-5618.2010.00815.x>. PMID: 20565430.
12. Berwaerts J, Melkote R, Nuamah I, et al. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. *Journal of Affective Disorders*. 2012 May;138(3):247-58. doi: <http://dx.doi.org/10.1016/j.jad.2012.01.047>. PMID: 22377512.
13. Yildiz A, Guleryuz S, Ankerst DP, et al. Protein kinase C inhibition in the treatment of mania: a double-blind, placebo-controlled trial of tamoxifen. *Archives of General Psychiatry*. 2008 Mar;65(3):255-63. doi: <http://dx.doi.org/10.1001/archgenpsychiatry.2007.43>. PMID: 18316672.
14. Bahk WM, Shin YC, Woo JM, et al. Topiramate and divalproex in combination with risperidone for acute mania: a randomized open-label study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005 Jan;29(1):115-21. doi: <http://dx.doi.org/10.1016/j.pnpbp.2004.10.013>. PMID: 15610953.

15. Chengappa RKN, Schwarzman LK, Hulihan JF, et al. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *Journal of Clinical Psychiatry*. 2006 Nov;67(11):1698-706. PMID: 17196048.
16. Kushner SF, Khan A, Lane R, et al. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. *Bipolar Disorders*. 2006 Feb;8(1):15-27. PMID: 16411977.

Appendix H. Drug Treatments for Depression

Section 1. Sertraline vs. Lithium vs. Lithium + Sertraline

Appendix Table H1. Characteristics of eligible studies: sertraline for depression

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Altshuler, 2017 ¹ RCT Multisite US Government RoB High 28135846	N=142 Mean Age 39 Female 54% White 97% BP II 100% Outpatient	BP II; current major depressive episode. IDS-C \geq 22; CGI-BP \geq 3 on depression subscale; YMRS \leq 8; CGI-BP=1 on mania severity subscale Substance Abuse Other Mental Health (Nonresponsive to Lithium or Sertraline)	Sertraline target 100 mg/day	C1: Lithium target 900 mg/day C2: Sertraline+ Lithium target 100 mg/day+900 mg/day	16 weeks	Switch to hypomania or mania (YMRS \geq 14 + CGI-BP \geq 4) Treatment response (decrease of \geq 50% IDS-C OR decrease \geq 2 points CGI-BP depression) Adverse Events Withdrawal 56% (Non-relapse withdrawal 32%)

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H2. Summary risk of bias assessments: sertraline for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Sertraline vs. Lithium vs. Lithium + Sertraline	Altshuler, 20171 Government 28135846	High	Overall attrition 56%; only time to relapse or withdrawal outcomes used. Block randomization. Allocation concealment described. Blinded assessors; unblinded treatment physicians in communication with blinded physician. No discussion of missing data approaches for generalized mixed modeling. Log rank test.

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H3. Outcomes summary: sertraline for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Sertraline vs. Lithium vs. Lithium + Sertraline	Altshuler, 20171 28135846	Treatment response 16 weeks 62.7% overall NS across groups	NA	NA	Switching 16 weeks 14% overall NS across groups	NR

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H4. Strength of evidence assessment: sertraline for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Sertraline vs. Lithium vs. Lithium + Sertraline	Response16 wks Switching 16 wks	1 RCT (n=142)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 2. Venlafaxine vs. Lithium

Appendix Table H5. Characteristics of eligible studies: venlafaxine for depression

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Amsterdam, 2016 ² RCT Singesite US Government RoB Moderate 26892848 26803764 ³	N=129 Mean Age 43 Female 57% White 73% BP II 100% Outpatient	BP II; current major depressive episode. HAM-D _≥ 16 Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds Labs/Other Conditions (Nonresponsive to Venlafaxine or Lithium)	Venlafaxine max 375 mg/day min 75 mg/day	Lithium serum level 0.8 to 1.5 mmol/L	12 weeks	Response (HSRD reduction \geq 50% plus CGI/S=1) Remission (HSRD _≤ 8 plus CGI/S=1 or 2) HSRD CGI/SRS Adverse Events Withdrawal 29%
Amsterdam, 2008 ^{4, 5} Open label RCT Singesite US Government RoB High 18344727 18486235 ⁵	N=83 Mean Age 37 Female 57% White 82% BP II 100% Outpatient	BP II; current major depressive episode. HAM-D _≥ 18 Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds Labs/Other Conditions (Nonresponsive to Venlafaxine or Lithium)	Venlafaxine max 375 mg/day min 75 mg/day	Lithium serum level 0.8 to 1.5 mmol/L	12 weeks	Response (HAM-D reduction \geq 50%) Remission (HAM-D final \leq 8) HAM-D YMRS CGI Withdrawal 40%

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H6. Summary risk of bias assessments: venlafaxine for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Venlafaxine vs. Lithium	Amsterdam, 20162 Government 26892848 268037643	Moderate	Overall attrition 29%. Differential attrition between arms. No discussion of missing data approaches for Fischers test or generalized estimating equations.
	Amsterdam, 20084Government 18344727 184862355	High	Open-label study. Attrition 40%. Differential attrition.

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H7. Outcomes summary: venlafaxine for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Venlafaxine vs. Lithium	Amsterdam, 20162 26892848 268037643	Remission 12 weeks Venlafaxine 38/65 (58.5%) Lithium 18/64 (28.1%) Favors Venlafaxine p=0.0007 Response 12 weeks Venlafaxine 44/65 (67.7%) Lithium 22/64 (34.4%) Favors Venlafaxine p=0.0002	HAM-D 12 weeks Modeling Favors Venlafaxine p<0.0001 (Not interpretable to MID)	CGI/S 12 weeks Modeling Favors Venlafaxine p<0.0001	Switching 12 weeks NS	Reported no serious adverse events
	Amsterdam, 2008 ⁴ 18344727 18486235 ⁵	<u>Remission</u> 12 weeks Venlafaxine 28/43 (44.2%) Lithium 13/40 (7.5%) Favors Venlafaxine p=0.0005 <u>Response</u> 12 weeks Venlafaxine 26/43 (60.4%) Lithium 8/40 (20%) Favors Venlafaxine p=0.0005	<u>HAM-D 17</u> 12 weeks Modeling Favors Venlafaxine -4.51 (-8.36 to -0.66) P=0.015 Less than MID of at least 27.1% improvement, or 14/52	<u>CGI/S</u> 12 weeks Modeling Favors Venlafaxine p<0.009	<u>Switching</u> 12 weeks NS	SAE 1 in lithium group (not described) NS for withdraw due to adverse event

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H8. Strength of evidence assessment: venlafaxine for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Venlafaxine vs. Lithium	Response 12 wks Remission 12 wks Ham-D 12 wks CGI/S 12 wks	2 RCTs (n=212)	See table above	Moderate	Consistent	Direct	Imprecise	Insufficient (weighted toward single moderate rob study of 129)

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 3. Memantine + Valproate vs. Placebo + Valproate

Appendix Table H9. Characteristics of eligible studies: memantine for depression by year then first author

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Lee, 2014 ^{6, 7} RCT Multisite Asia Government RoB High 24103632/ 23870798	N = 232 Mean Age 32 Female 49% Race NR BP II 100% Inpatient and/or Outpatient (NR)	Modified BP II (2-days hypomanic versus 4-days used in DSM-IV criteria); HAM-D \geq 18 Schizoaffective Substance abuse Other mental health Neurological disorders Taking other medications	Memantine 5 mg/ daily + Valproate 500-1000 mg/day	Placebo + Valproate 500-1000 mg/day	12 weeks	YMRS HAM-D Withdrawal 32%

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H10. Summary risk of bias assessments: memantine for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Memantine + valproate vs. placebo + valproate	Lee, 2014 ^{6, 7} Government 24103632	High	Randomization and blinding procedures not described; Inpatient and outpatient settings of patients not described or included in analysis, creating a residual confounder; baseline YMRS score not balanced between arms and not included in modelling analysis; handling of attrition not described

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H11. Outcomes summary: memantine for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Memantine + valproate vs. placebo + valproate	Lee, 2014 ^{6,7} 24103632	NR	<u>HAM-D</u> 12 week NS p=0.363 <u>YMRS</u> 12 week NS p=0.115	NR	NR	NR

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H12. Strength of evidence assessment: memantine for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Memantine + valproate vs. placebo + valproate	HAM-D 12 wks	1 RCT (n=232)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 4. Lamotrigine + Mood Stabilizers vs. Placebo + Mood Stabilizers

Appendix Table H13. Characteristics of eligible studies: lamotrigine for depression

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Kemp, 2012 ⁸ RCT Single US Gov't+nonprofit ROB Moderate 23107222	N=49 Mean Age 50 Female 56% White 92% BP I 55% BP II 45%	BPI or II; rapid cycling in previous 12 months; MADRS _≥ 20 Substance Abuse Other Mental Health Pregnant/Nursing Taking Other Meds (nonresponsive to lamotrigine previously)	Lamotrigine 15-200 mg/day + Lithium or divalproex	Placebo + Lithium or divalproex	12 weeks	MADRS CGI-S YMRS Response (MADRS _≥ 50% decrease) Remission (MADRS _≤ 10) Bimodal response (MADRS _≤ 19, YMRS _≤ 12, GAF _≥ 51) Withdrawal 17%

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H14. Summary risk of bias assessments: lamotrigine for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lamotrigine + mood stabilizers vs. placebo + mood stabilizers	Kemp, 2012 ⁸ Gov't+nonprofit 23107222	Moderate	Randomization and blinding procedures not described. 16% withdrawal.

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H15. Outcomes summary: lamotrigine for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Lamotrigine + mood stabilizers vs. placebo + mood stabilizers	Kemp, 2012 ⁸ Gov't+nonprofit 23107222	<u>Remission</u> 12 weeks Lamotrigine: 3/23 Placebo: 8/26 NS <u>Response</u> 12 weeks Lamotrigine: 2/23 Placebo: 10/38 p=0.02 <u>Bimodal</u> 12 weeks Lamotrigine: 7/23 Placebo: 8/26 NS	NR	NR	Withdrawal for nonresponse or clinical worsening: Treat:4 Placebo:4	<u>Severe AE</u> NS Lamotrigine: 1 suicidality, 1 depression hospitalization Placebo: none reported Switching: 2 placebo patients

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H16. Strength of evidence assessment: lamotrigine for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lamotrigine + mood stabilizers vs. placebo + mood stabilizers	Remission 12 wks Response 12 wks Bimodal remission/response 12 wks	1 RCT (n=133)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 5. Antidepressants vs. Placebo

Appendix Table H17. Characteristics of eligible studies: antidepressants for depression

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Sachs, 2007 ⁹ RCT Multisite 1 Continent Government High 17392295	N = 366 Mean Age 40 Female 57% White 90% BP I 68% BP-II 32% Outpatient	Major Depressive Episode Substance Abuse Other Mental Health Taking Other Meds Labs/Other Conditions	Paroxetine Initiated at 10mg/day increased up to 40mg/day Bupropion Initiated at 150mg/day increased to maximum 375mg.day	Placebo	26 weeks	SUM-D SUM-ME MADRS YMRS GAF CGI Adverse Events Withdrawal 44%

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H18. Summary risk of bias assessments: Antidepressants for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Antidepressives vs. placebo	Sachs, 2007 ⁹ Government 17392295	High	Participants were switched to open label after a severe response and they remained in the study, psychotherapies were included and not measured as a confounding effect, and they pool results for all mood stabilizers and antidepressants. 44% attrition

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H19. Outcomes summary: antidepressants for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Antidepressives vs. placebo	Sachs, 2007 ⁹ Government 17392295	<u>Durable recovery</u> 26 weeks NS <u>Transient remission</u> 26 weeks NS	NR	NR	Withdrawal due to clinical worsening: Treat: 34.1% Placebo:33.7% Withdrawal w/out reaching clinical outcome: Treat:6.7% Placebo:7%	<u>Severe AE</u> NS Antidepressants: 8 (4.5%) Placebo: 10 (5.3%) Included (antidepressants, placebo): medical hospitalization(8,1), medical illness(0,2), psychiatric hospitalization for depression or suicidal ideation(6,6), or nonbipolar symptoms(2,1), or increased suicidal ideation without hospitalization(0,1) Switching (10.1%, 10.7%) No reported deaths

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H20. Strength of evidence assessment: antidepressants for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Antidepressives vs. placebo	Durable recovery 26 wks Transient remission 26 wks Discontinuation 26 wks	1 RCT (n=366)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 6. Lithium

Appendix Table H21. Characteristics of eligible studies: lithium depression

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Nierenberg, 2013 ¹⁰ RCT Multisite US Government RoB Low 23288387	N=283 Mean Age 39 Female 56.5% White 75% African American 17% BP I 76% BP II 24% Outpatient	Currently symptomatic (not defined), requiring a change in medication (Mean YMRS 12.5; MADRS 22.5; CGI severity 4.3) Current lithium use Need for hospitalization Other Medical Conditions Pregnancy	Lithium 600 mg/day for first 2 months; thereafter adjusted as clinically needed + Optimized Personalized Treatment	Optimized Personalized Treatment	6 months	CGI-BP-S Necessary Clinical Adjustments (study-defined – all medication adjustments needed to respond to clinical need) MADRS YMRS CGI-BP-S LIFE-RIFT Remission Withdrawal 16%

Abbreviations: BP=bipolar disorder; C=Comparison; CGI=Clinical Global Impressions Scale; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Revision; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HSRD=Hamilton Rating Scale for Depression; IDS-C=Inventory for Depressive Symptoms(Clinician-Rated); MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; ROB=risk of bias; SRS=symptom rating scale; SUM-D=Symptom Subscale for Depression; SUM-ME=Symptom Subscale for Mood Elevation; YMRS = Young Mania Rating Scale

Appendix Table H22. Summary risk of bias assessments: lithium for depression

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lithium	Nierenberg, 2013 ¹⁰ Government 23288387	Low	Open-label but rater blinded.

Abbreviations: PMID=PubMed Identification Number; YMRS=Young Mania Rating Scale

Appendix Table H23. Outcomes summary: lithium for depression

Drug	Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium + Optimized Personalized Treatment (OPT) vs. OPT	Nierenberg, 2013 ¹⁰ Low 23288387	Remission 6 months NS	Necessary Clinical Adjustment 6 months NS Lithium+OPT 1.01 OPT 0.99 YMRS 6 months NS Lithium+OPT -6.35 OPT -5.79 MADRS 6 months NS Lithium+OPT -8.20 OPT -8.84	CGI-BP-S 6 months NS Lithium+OPT -1.2 OPT -1.5	Overall Withdrawal Lithium+OPT 17.7% OPT 14.8%	SAE Reported no difference between groups No deaths Suicidal Ideation No difference between groups

Abbreviations: AE=Adverse Events; CGI=Clinical Global Impressions Scale; HAM-D=Hamilton Scale for Depression; MID=minimally important difference; NA=Not applicable; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS =Young Mania Rating Scale

Appendix Table H24. Strength of evidence assessment: lithium for depression

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lithium + OPT vs. OPT alone	CGI Clinical Need MADRS YMRS Remission	1 RCT (n=283)	See table above	Low	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; HAM-D=Hamilton Scale for Depression; n=number of subjects; RCT=randomized controlled trial

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

References for Appendix H

1. Altshuler LL, Sugar CA, McElroy SL, et al. Switch rates during acute treatment for Bipolar II depression with Lithium, Sertraline, or the two combined: A randomized double-blind comparison. *American Journal of Psychiatry*. 2017 March;174(3):266-76. doi: <http://dx.doi.org/10.1176/appi.ajp.2016.15040558> . PMID: 28135846 PMID/614689619 Embase.
2. Amsterdam JD, Lorenzo-Luaces L, Soeller I, et al. Short-term venlafaxine v. lithium monotherapy for bipolar type II major depressive episodes: Effectiveness and mood conversion rate. *British Journal of Psychiatry*. 2016 April;208(4):359-65. doi: <http://dx.doi.org/10.1192/bjp.bp.115.169375>. PMID: 26892848 PMID/609914520 Embase.
3. Lorenzo-Luaces L, Amsterdam JD, Soeller I, et al. Rapid versus non-rapid cycling bipolar II depression: Response to venlafaxine and lithium and hypomanic risk. *Acta Psychiatrica Scandinavica*. 2016 01 Jun;133(6):459-69. doi: <http://dx.doi.org/10.1111/acps.12557>. PMID: 26803764 PMID/608565179 Embase.
4. Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. *J Clin Psychopharmacol*. 2008 Apr;28(2):171-81. doi: 10.1097/JCP.0b013e318166c4e6. PMID: 18344727.
5. Amsterdam JD, Wang CH, Shwarz M, et al. Venlafaxine versus lithium monotherapy of rapid and non-rapid cycling patients with bipolar II major depressive episode: a randomized, parallel group, open-label trial. *Journal of Affective Disorders*. 2009 Jan;112(1-3):219-30. doi: <http://dx.doi.org/10.1016/j.jad.2008.03.029>. PMID: 18486235.
6. Lee SY, Chen SL, Chang YH, et al. Genotype variant associated with add-on memantine in bipolar II disorder.[Erratum appears in *Int J Neuropsychopharmacol*. 2014 Jun;17(6):979 Note: Lu, Ru-Band [removed]; Hong, Jau-Shyong [added]]. *International Journal of Neuropsychopharmacology*. 2014 Feb;17(2):189-97. doi: <http://dx.doi.org/10.1017/S1461145713000825>. PMID: 24103632.
7. Lee S-Y, Chen S-L, Chang Y-H, et al. Add-on memantine to valproate treatment increased HDL-C in bipolar II disorder. *Journal of Psychiatric Research*. 2013 2013;47(10):1343-8. doi: <http://dx.doi.org/10.1016/j.jpsychires.2013.06.017> . PMID: 23870798.
8. Kemp DE, Gao K, Fein EB, et al. Lamotrigine as add-on treatment to lithium and divalproex: lessons learned from a double-blind, placebo-controlled trial in rapid-cycling bipolar disorder. *Bipolar Disorders*. 2012 Nov;14(7):780-9. doi: <http://dx.doi.org/10.1111/bdi.12013>. PMID: 23107222.
9. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *The New England Journal of Medicine*. 2007;356(17):1711-22. doi: <http://dx.doi.org/10.1056/NEJMoa064135>. PMID: 17392295.
10. Nierenberg AA, Friedman ES, Bowden CL, et al. Lithium treatment moderate-dose use study (LiTMUS) for bipolar disorder: a randomized comparative effectiveness trial of optimized personalized treatment with and without lithium. *American Journal of Psychiatry*. 2013 Jan 1;170(1):102-10. doi: <http://dx.doi.org/10.1176/appi.ajp.2012.12060751> . PMID: 23288387.

Appendix I. Drug Treatments for Maintenance

Section 1. Lithium Monotherapy vs. Inactive Controls

Appendix Table I1. Characteristics of eligible studies: lithium monotherapy for maintenance

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Bowden, 2000 ¹ RCT Multisite US Industry RoB High 10807488 12784116 ²	N=372 Mean Age 39 Female 51% White 94% BP I 100% Outpatient	No Episode at Randomization; Scores of MRS ≤ 11, DSS ≤ 13, GAS > 60; At least one other manic episode in past three years. Substance Abuse; Other Mental Health Conditions; Taking Other Medications; Pregnant/Nursing	Divalproex 71-125 mcg/mL (Mean 84.8 mcg/mL) N= 187	C1: Placebo n= 92 C2: Lithium 0.8-1.2 mEq/L (Mean 0.9 mEq/L) n= 90	52 week	Time to recurrence, any Time to recurrence, mania (MRS≥16) Time to recurrence, depression (DSS≥25) Withdrawal 69% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 40%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Amsterdam, 2010 ³ RCT Single-site US Gov't+nonprofit RoB Moderate 20360317	N =81 Mean Age 38 Female 52% White NR BP II 100% Outpatient	Depression and HAM-D \geq 16 initially; then HAM-D \leq 8 after 12 weeks of initial Fluoxetine therapy at 20-80mg/day) Substance abuse Neurological Disorders Taking other medications Pregnant/NursingLabs/Other Conditions	Fluoxetine (n=28) 10-40 mg/day (mean 34.3 mg/day) N=28	C1: Placebo (n=27) C2: Lithium (n=26) 300-1200 mg/day; 0.5-1.5 mmol/L (mean 1027 mg/day; 0.69 mmol/L)	50 weeks	YMRS Relapse (HAM-D \geq 14) Adverse Events Lab Values Withdrawal 72% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 25%
Bowden, 2003 ⁴ RCT of responders Multisite 2 continents Industry RoB Low 12695317	N=175 Mean Age 41 Female 47% Race NR BP I 100% Outpatient	Lamotrigine responders (CGI-S \leq 3 for at least 4 continuous weeks) For open label period: Manic; DSM-IV Criteria for Mania or Hypomania currently or within past 60 days with previous episodes in past 3 years Other Mental Health Conditions	Lamotrigine 100-400 mg/day (Mean NR) N=59	C1: Placebo N=70 C2: Lithium 0.8-1.1 mEq/L Mean NR N=59	18 Months	Time to intervention for mania, hypomania, mixed, depression, and any mood episodes Time to early discontinuation Adverse Events I Withdrawal 80% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Calabrese, 2003 ⁵ RCT of responders Multisite 4 Continents Industry RoB Moderate 14628976	N=410 Mean Age 43 Female 56% Race NR BP I 100% Outpatient	Lamotrigine responders (CGI-S<3 for at least 4 continuous weeks) For open label period: depression; DSM-IV criteria for depression currently or within past 60 days with previous depression and mania episodes in past 3 years. Other Mental Health Conditions	Lamotrigine 50, 200, or 400 mg/day (in analysis 50mg group was censored, 200 and 400 mg/day groups were combined) N=221	C1: Placebo N=121 C2: Lithium 0.8-1.1 mEq/L (Mean 0.8 mEq/L) N=121	18 Months	Time to intervention for mania, hypomania, depression, any mood episode Time to early discontinuation Adverse Events Withdrawal 84.9% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 34%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Prien, 1973 ⁶ RCT Multisite US Government RoB High 4569674	N=205 Median Age 44 Sex NR Race NR BP I 100% Outpatient	No Episode at Randomization; Neurological Disorders; Abnormal Lab Results	Lithium 0.5-1.4 mEq/L (Mean 0.7 mEq/L)	Placebo	2 years	Relapse, type/proportion (manic, mixed, schizoaffective, depressive event requiring hospitalization 'severe' or supplementary drugs 'moderate') Time to early discontinuation GAS IMPS (Inpatient Multidimensional Psychiatric Scale) Self-Report Mood Scale KAS (Katz Adjustment Scale) Adverse Events Withdrawal 42%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Weisler, 2011 ⁷ RCT Multisite 5 continents Industry RoB Moderate 22054050	N=1226 Mean Age 40 Female 53% White 63% BP 1 100% Outpatient	Meeting stability criteria of YMRS \leq 12 and MADRS \leq 12 after last episode of depression/mania/mixed episode at study entry or within past two years Substance Abuse Other Mental Health Conditions Pregnant/Nursing Labs/Other Conditions	Quetiapine 300-800 mg/day (543 mg/day mean) N=404	C1: Placebo N=404 C2:Lithium 600-1800 mg/day 0.6-1.2 mEq/L (0.63 mEq/L mean) N=364	104 weeks	Time to recurrence any mood (algorithm) Time to manic event Time to depressive event Time to all-cause discontinuation SDS MOS-Cog CGI-BP PANNS-P WPAI TMT Withdrawal 55% (Time to recurrence outcomes only included) Nonrelapse withdrawal 22%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BIS-11=Barratt Impulsiveness Scale; BMI=Body Mass Index; BP=bipolar disorder; C=Comparison; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-M=Clinical Global Impressions Scale-Bipolar-modified (for long-term follow-up); CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-EI=Clinical Global Impressions-Efficacy Index; CGI-I=Clinical Global Impressions Scale, Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSS=Depressive Syndrome Scale; EPS=extrapyramidal symptoms; ESRs=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; IMPS=Inpatient Multidimensional Psychiatric Scale; KAS=Katz Adjustment Scale; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MOS-Cog=Medical Outcomes Study Cognitive Scale; MRS=Mania Rating Scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PGWB=Psychological General Well-being Scale; PMID=PubMed Identification Number; PSQI=Pittsburgh Sleep Quality Index; QIDS-SR=Quick Inventory of Depressive Symptomatology (Self-reported); RCT=randomized controlled trial; ROB=risk of bias; SAS=Simpson Angus Scale; SDS=Sheehan Disability Scale; TMT=Trail Making Test; WPAI=Work Productivity and Activity Impairment Questionnaire; YMRS =Young Mania

Appendix Table I2. Summary risk of bias assessments: Lithium monotherapy for maintenance

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lamotrigine vs. Lithium vs. placebo	Bowden, 2003 ⁴ Industry 12695317	Moderate (High for log rank test)	Randomization and blinding procedures not described. Balanced traits among groups at baseline. Efficacy data may be biased by dropout as endpoints are LOCF and differential nonrelapse dropout rates that range from 16-25% of patients for each arm.
	Calabrese, 2003 ⁵ Industry 14628976	Moderate (High for log rank test)	Randomization and allocation concealment not described. Balanced traits among groups at baseline. Efficacy data may be biased by dropout as endpoints are LOCF. 34% withdrawal.
Fluoxetine vs. lithium vs. placebo	Amsterdam, 2010 ³ Government/Non profit 20360317	Moderate	Randomization may not have been successful as it relates to a person's likelihood of relapse; randomization, allocation, and blinding procedures are underdescribed. 23% dropout.
Divalproex vs. lithium vs. placebo	Bowden, 2000 ¹ Industry 10807488 12784116 ²	High	Appears to be unblinded. Randomization not described. Nonrelapse dropout of 40%.
Lithium vs. placebo	Prien, 1973 ⁶ Government 4569674	High	Differential dropout rate is significant. Study didn't demonstrate allocation concealed.
Quetiapine vs. lithium vs. placebo + lithium	Weisler, 2011 ⁷ Industry 22054050	Moderate	Generally a well conducted and reported study, however some sources of bias present related to dropout rates. Overall 21% withdraw due to reasons unrelated to recurrence; however by week 16 more than 50% of the placebo group has dropped for all causes, as well as 40% of the lithium group and 25% of the quetiapine group)

Abbreviations: BP=bipolar; LOCF=Last observation carried forward; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table I3. Outcomes summary table: lithium monotherapy versus placebo for maintenance

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium vs. placebo	Bowden, 2000 ¹ 10807488 12784116 ²	Time to any recurrence 12 months NS Time to mania recurrence 12 months NS Time to depression recurrence 12 months NS	NA (Exclude for attrition = 69%)	<u>NR</u>	<u>NR</u>	<u>SAE</u> NR <u>Tremor</u> Lithium 42% (38/94) Placebo 13% (12/94) Favors Placebo p<0.001 <u>Akathisia</u> Lithium 4% (4/94)Placebo 1% (1/94) NS
	Amsterdam, 2010 ³ 20360317	<u>Time to Relapse to Depression</u> 50 week Log rank NS	<u>NA</u> (Exclude for attrition = 72%)	NR	NR	<u>SAE</u> Reported no events <u>EPS</u> Reported no events
	Bowden, 2003 ⁴ 1269531	<u>Time to any recurrence</u> 18 months Log rank Favors Lithium p=0.001 <u>Time to mania recurrence</u> 18 months Log rank Favors Lithium p=0.006 <u>Time to depression recurrence</u> 18 months Log rank NS	NA (Exclude for attrition = 80%)	NA	NA	<u>SAE</u> No events reported <u>Suicidality per HAM-D</u> NS between groups <u>Tremor</u> Lithium 42% (38/94) Placebo 13% (12/94) Favors Placebo P<0.001 <u>Akathisia</u> Lithium 4% (4/94) Placebo 1% (1/94) NS

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
	Calabrese, 2003 ⁵ 14628976	<u>Time to any recurrence</u> 18 months Log rank Favors Lithium p=0.03 <u>Time to mania recurrence</u> 18 months Log rank NS <u>Time to depression recurrence</u> 18 months Log rank NS	NA (Exclude for attrition = 85%)	NA	NA	<u>SAE</u> 1 death in lamotrigine groups <u>Suicidality per HAM-D</u> NS between groups <u>Tremor</u> Lithium 17% (20/120) Placebo 5% (6/121) Favors Placebo P<0.05
	Prien, 1973 ⁶ High 4569674	<u>Relapse, any episode type</u> (manic, mixed, schizoaffective, depressive event requiring hospitalization or supplementary drugs) Lithium 43% (43/101) Placebo 80% (84/104) Favors Lithium p<0.001	NR	NR	Suicide Placebo 1/104 Overall Withdrawal Lithium 27% (27/101) Placebo 57% (59/104) Favors lithium p<0.001 Withdrawal due to 'poor clinical response' (further participation would seriously jeopardize the patients physical or mental health) Lithium 11% (11/101) Placebo 40% (41/104)	<u>SAE</u> Lithium 24% (24/101) Placebo 0% (assumed - none reported) Lithium: 3/101 – Toxicity (1) Hypothyroidism with goiter, polyuria, polydipsia (1) Hypothyroidism w/o goiter (3) Leukocytosis (1) <u>Death</u> Lithium 1/101 Placebo 1/104

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
	Weisler, 2011 ⁷ 22054050	<u>Time to recurrence of any mood event</u> Favors Lithium HR 0.46 (95% CI 0.36, 0.59), p<0.0001 <u>Time to recurrence of manic event</u> Favors Lithium HR 0.37 (95% CI 0.27, 0.53), p<0.0001 <u>Time to recurrence of depression symptoms</u> Favors Lithium HR 0.59 (95% CI 0.42, 0.84), p<0.004	<u>NA</u> (Exclude for attrition 55%)	NR	<u>NR</u>	<u>SAE</u> 10 lithium 11 placebo <u>EPS</u> 38 lithium 18 placebo No deaths

Abbreviations: AE=Adverse Events; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; HAM-D=Hamilton Scale for Depression; HR=Hazard Ratio; LSM=least-squares means; MADRS=Montgomery-Asberg Depression Rating Scale; NA=Not applicable; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table I4. Strength of evidence assessment: lithium monotherapy versus placebo for maintenance

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lithium vs. placebo	Time to overall relapse 1-2 yrs	6 RCT (n=1579)	Favors Lithium 1 to 2 years	Moderate	Consistent	Direct	Imprecise	Low (weighted by moderate study and hazard ratio)
Lithium vs. placebo	Time to manic or depressive relapse 1-2 yrs	6 RCT (n=1579)	See table above	Moderate	Inconsistent	Direct	Imprecise	Insufficient

Abbreviations: MADRS=Montgomery-Asberg Depression Rating Scale; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 2. Other Monotherapy

Appendix Table I5. Characteristics of eligible studies: other monotherapy for maintenance by year then first author

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Calabrese, 2017 ⁸ RCT Multisite 4 Continents Industry RoB Moderate 28146613	N=266 Mean Age 41 Female 58% Race White 54% Black/African American 28% BP I 100% Inpatient/Outpatient	≥1 previous manic or mixed episode severity requiring hospitalization or treatment with mood stabilizer or treatment with antipsychotic agent. Current episode YMRS ≥20 but then met YMRS ≤12, MADRS ≤12, no active suicidality Rapid Cycling Refractory BP First Manic Episode Substance Abuse Other Mental Health Labs/Other Conditions	Aripiprazole once-monthly injections 400 mg	Placebo	52 week	Time to recurrence (hospitalization or YMRS >15; MADRS >15; CGI- BP >4; further medication; suicidality) Proportion meeting recurrence YMRS MADRS Withdrawal 61.7% (nonrelapse withdrawal 23%)
Keck, 2006 ⁹ RCT Multisite 2 Continents Industry Rob Moderate 16669728	N=161 Mean Age 40; Female 67% Race White 56% Hispanic/Latino 23% BP I 100% Outpatient	Symptom stability: YMRS ≤10 and MADRS ≤13 for 4 consecutive visits over 6 weeks Substance Abuse Other Mental Health Labs/Other Conditions Pregnant/Nursing Unresponsive to Clozapine ECT in last 2 years	Aripiprazole 15 or 30 mg/day based on investigator discretion	Placebo	26 weeks	Time to relapse (defined as lack of efficacy) YMRS MADRS PANSS CGI-BP Withdrawal 58% (nonrelapse withdrawal 24%)

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Hartong, 2003 ¹⁰ RCT Multisite Netherlands Industry/Government RoB Low 12633122	N = 98 Mean Age 42 Female 54% Race NR BP I 77% BP-II 23% Outpatient	Remission from any Episode Type; According to Bech Rafaelsen Mania or Melancholia Scales First Manic Episode	Carbamazepine 6-10 mg/L (6.8 mg/L average)	Lithium 0.6-1 mmol/L (0.75 mmol/L average)	2 years	Remission (YMRS <=12) Response (50% decrease in YMRS) Efficacy YMRS CGI-BP-S MADRS Adverse events Extrapyramidal symptoms SAS AIMS BARS Withdrawal 31%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Greil, 1997 ¹¹ RCT Multisite Germany Government RoB High 9165384 also 9864077 ¹² 10529070 ¹³ 10529071 ¹⁴ 11093063 ¹⁵	N = 171 Mean Age 40 Female 57% Race NR BP I 58% BP-NOS 33% Outpatient	Remission from any Episode Type; GAS > 70 First Manic Episode Substance Abuse Other Mental Health Neurological Disorders	Carbamazepine 635 mg/day	Lithium 26.8 mmol/day	2 years (130 weeks?)	Remission (YMRS <=12) Response (50% decrease in YMRS) Efficacy YMRS CGI-BP-S MADRS Adverse events Extrapyramidal symptoms SAS AIMS BARS Withdrawal 23%
Calabrese, 2005 ¹⁶ RCT of responders US Government ROB Moderate 16263857	N=60 Mean Age 37 Female 52% White NR BP I 60% BP-II 40% Outpatient	Responders to both drugs Rapid cycling; mood episode in previous 3 months Substance Use Other Mental Health Conditions Pregnant/Nursing Lab/other conditions Intolerant of lithium	Divalproex/valproate mean divalproex dose 1571 mg/day; mean valproate dose 77	Lithium mean lithium dose 1359 mg/day	20 month	Time to relapse (HAM- D ≥20 or YMRS ≥20 for 8 weeks) Withdrawal 88% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Bowden, 2000 ¹ RCT Multisite US Industry RoB High 10807488 12784116 ²	N=372 Mean Age 39 Female 51% White 94% BP I 100% Outpatient	No Episode at Randomization; Scores of MRS \leq 11, DSS \leq 13, GAS > 60; At least one other manic episode in past three years. Substance Abuse; Other Mental Health Conditions; Taking Other Medications; Pregnant/Nursing	Divalproex 71-125 mcg/mL (Mean 84.8 mcg/mL) N= 187	C1: Placebo n= 92 C2: Lithium 0.8-1.2 mEq/L (Mean 0.9 mEq/L) n= 90	52 week	Time to recurrence, any Time to recurrence, mania (MRS \geq 16) Time to recurrence, depression (DSS \geq 25) Withdrawal 69% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 40%
Amsterdam, 2010 ³ RCT Single-site US Gov't+nonprofit RoB Moderate 20360317	N =81 Mean Age 38 Female 52% White NR BP II 100% Outpatient	Depression and HAM-D \geq 16 initially; then HAM-D \leq 8 after 12 weeks of initial Fluoxetine therapy at 20-80mg/day) Substance abuse Neurological Disorders Taking other medications Pregnant/Nursing/Labs/Other Conditions	Fluoxetine (n=28) 10-40 mg/day (mean 34.3 mg/day) N=28	C1: Placebo (n=27) C2: Lithium (n=26) 300-1200 mg/day; 0.5-1.5 mmol/L (mean 1027 mg/day; 0.69 mmol/L)	50 weeks	YMRS Relapse (HAM-D \geq 14) Adverse Events Lab Values Withdrawal 72% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Bowden, 2003 ⁴ RCT of responders Multisite 2 continents Industry RoB Low 12695317	N=175 Mean Age 41 Female 47% Race NR BP I 100% Outpatient	Lamotrigine responders (CGI-S _≤ 3 for at least 4 continuous weeks) For open label period: Manic; DSM-IV Criteria for Mania or Hypomania currently or within past 60 days with previous episodes in past 3 years Other Mental Health Conditions	Lamotrigine 100-400 mg/day (Mean NR) N=59	C1: Placebo N=70 C2: Lithium 0.8-1.1 mEq/L Mean NR N=59	18 Months	Time to intervention for mania, hypomania, mixed, depression, and any mood episodes Time to early discontinuation Adverse Events I Withdrawal 80% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 20%
Calabrese, 2003 ⁵ RCT of responders Multisite 4 Continents Industry RoB Moderate 14628976	N=410 Mean Age 43 Female 56% Race NR BP I 100% Outpatient	Lamotrigine responders (CGI-S _{<} 3 for at least 4 continuous weeks) For open label period: depression; DSM-IV criteria for depression currently or within past 60 days with previous depression and mania episodes in past 3 years. Other Mental Health Conditions	Lamotrigine 50, 200, or 400 mg/day (in analysis 50mg group was censored, 200 and 400 mg/day groups were combined) N=221	C1: Placebo N=121 C2: Lithium 0.8-1.1 mEq/L (Mean 0.8 mEq/L) N=121	18 Months	Time to intervention for mania, hypomania, depression, any mood episode Time to early discontinuation Adverse Events Withdrawal 84.9% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 34%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Calabrese, 2000 ¹⁷ RCT of responders Multisite US, Canada Industry ROB High 11105737	N=182 Mean Age 38 Female 58% Race NR BP I 70% BP-II 30% Outpatient	Rapid cyclers, stabilized on lamotrigine (no mood episodes requiring other drugs or ECT) Other Mental Health Conditions Labs/Other conditions	Lamotrigine 100-500 mg/day N=93	Placebo N=89	26 weeks	Time to addition drug treatment Time to overall withdrawal Withdrawal 67% (Time to recurrence outcomes only included) Nonrelapse withdrawal 15%
Balance Investigators, 2010 ¹⁸ RCT Multisite US and Europe Industry RoB Moderate 20092882	N=330 Mean Age 43 Female 49% Race NR BP I 100% Outpatient	Not having acute episode; Not defined Pregnant/Nursing	Lithium 0.4-1.0 mmol/L mean NR + Valproate 750-1250 or highest tolerated mean NR n=110	C1: Lithium 0.4-1.0 mmol/L mean NR N=110 C2: Valproate 750-1250 or highest tolerated mean NR n=110	24 months	GAF EuroQoL (EQ-5D) (quality of life) Relapse Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2006 ¹⁹ RCT Multisite 2 Continents Industry RoB Moderate 16449478	N= 361 Mean Age 41 Female 39% White 87% BP I 100% Outpatient	Remission; YMRS \leq 12 HAM-D \leq 8 First Manic Episode	Olanzapine 5–20 mg/day	Placebo	48 weeks	Time to Relapse Symptom Severity YMRS HAM-D Adverse Events Withdrawal 84% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 25%
Tohen, 2003 ²⁰ RCT Multisite US Industry ROB High 12832240 Extension of Tohen, 2002b ²¹ 12042191	N=251 Mean Age 40 Female 57% White 82% BP-I 100% Outpatient	YMRS >19 Substance Use Pregnant/Nursing Labs/other conditions	Olanzapine 5-20 mg/day	Divalproex 500-2500 mg/day	42 weeks	Time to relapse Withdrawal 84% (Time to relapse only included) Nonrelapse withdrawal unclear

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Quiroz, 2010 ²² RCT of Responders Multisite 3 Continents Industry ROB Moderate 20227682	N=303 Mean Age 39 Female 49% White 80% BP-I 100% Outpatient	Responders to Phase III: stable at CGI-BP-S <3 Substand abuse Taking other meds Pregnant/nursing Rapid cycling Other mental health Labs/other conditions	Risperidone long- acting injectable 25, 37.5, or 50 mg; 77% received 25mg/2 weeks N=154	Placebo N=149	24 months	Time to recurrence of mood episode Time to: elevated mood depressive early discontinue due to medications Efficacy YMRS MADRS CGI-S Withdrawal 66% (Time to recurrence outcomes only) Nonrelapse withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Vieta, 2012 ²³ RCT of Responders Multisite 3 Continents Industry RoB High 22503488	N = 398 Mean Age 36 Female 52% White 45% BP 1 100% Outpatient	No recurrence event (Responders from Phase II): Not hypomanic, manic, mixed, or depressive episode; treatment with a mood stabilizer, antidepressant or prohibited antipsychotic and benzodiazepine usage; hospitalization for a mood episode; or CGI-S \geq 4 with either YMRS $>$ 12 or MADRS $>$ 12 First Manic Episode Schizoaffective Other Mental Health Taking Other Meds Pregnant/Nursing	Risperidone long- acting injectable 1-6mg/day (fixed dose distribution provided; 25mg/2 weeks 64%, 37.5mg/2weeks 32%; 50mg/2 weeks 4%) N=131	C1: Placebo N=133 C2: Olanzapine 10mg/day N=130	18 months	Response (YMRS \leq 19) Time to first recurrence of mood symptoms Efficacy YMRS CGI-S MADRS Adverse events Extrapyramidal symptoms ESRS Withdrawal 58% (Time to recurrence outcomes only included) Nonrelapse withdrawal 29%
Tohen, 2005 ²⁴ RCT Multisite 5 Continents Industry RoB Moderate 15994710	N= 431 Mean Age 42 Female 53% White 99% BP NR Outpatient	Met remission criteria: including YMRS \leq 15 and HAM-D \leq 8 After open-label period: Manic or Mixed Episode YMRS \geq 20 Substance Abuse Other Mental Health Neurological Disorders Taking Other Meds Labs/Other Conditions	Olanzapine 15 mg/day flexible dosing 5–20 mg/day	Lithium 600 mg/day flexible dosing for blood level 0.6–1.2 meq/liter	52 weeks	Time to Episode Adverse Events Extrapyramidal Symptoms Withdrawal 60% (Time to recurrence outcomes only included) Nonrelapse Withdrawal 30%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Berwaerts, 2012 ²⁵ RCT Multisite 5 Continents Industry RoB High 22377512	N = 383 Mean Age 40 Female 53% White 60% BP I 100% Outpatient	Remission; YMRS and MADRS ≤12 for last three weeks of acute and continuation treatment study phases First manic episode Schizoaffective Substance abuse Other mental health Neurological disorders Labs/other conditions	Paliperidone EX 3-12 mg/day (n=152)	C1: Placebo (n=148) C2: Olanzapine 5-20 mg/day – few usable outcomes N=83	Up to 3 years (until recurrence)	YMRS Relapse (HAM-D ≥14) Adverse Events Lab Values Withdrawal 38%
Amsterdam, 2015 ²⁶ RCT extension of responders Single Site US Government RoB High 26143402	N = 55 Mean Age 42 Female 54% White 17% BP II 100% Outpatient	Responders to RCT phase: >50% reduction in baseline HAM-D + CGI-BP-S <3 Substance abuse Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions	Venlafaxine 75-375 mg/day (mean 253.9 mg/day)	Lithium 300-1200 mg/day (Serum level of 0.8-1.5 mEq/L)	6 months	Relapse (HAM-D >14+CGI>3 for at least 14 days) Relapse hazard Time to relapse YMRS Withdrawal 18% (after 43% attrition from acute treatment)

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Newport, 2008 ²⁷ Observational Single Site 1 Continent Government/Nonprofit High 18402631	N=26 Mean Age NR Female 100% White 91% BP I 73% BP-II 23% BP-NOS 4% Outpatient	Euthymic at conception Labs/Other Conditions	Lamotrigine Average 252 mg/day	Mood Stabilizer Discontinuation Initial doses Divalproex: 1200 mg/day average Lithium: 825 mg/day average Lamotrigine: 190 mg/day average	40 weeks	Survival Time Withdrawal NR

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Weisler, 2011 ⁷ RCT Multisite 5 continents Industry RoB Moderate 22054050	N=1226 Mean Age 40 Female 53% White 63% BP 1 100% Outpatient	Meeting stability criteria of YMRS \leq 12 and MADRS \leq 12 after last episode of depression/mania/mixed episode at study entry or within past two years Substance Abuse Other Mental Health Conditions Pregnant/Nursing Labs/Other Conditions	Quetiapine 300-800 mg/day (543 mg/day mean) N=404	C1: Placebo N=404 C2:Lithium 600-1800 mg/day 0.6-1.2 mEq/L (0.63 mEq/L mean) N=364	104 weeks	Time to recurrence any mood (algorithm) Time to manic event Time to depressive event Time to all-cause discontinuation SDS MOS-Cog CGI-BP PANNS-P WPAI TMT Withdrawal 55% (Time to recurrence outcomes only included) Nonrelapse withdrawal 22%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BIS-11=Barratt Impulsiveness Scale; BMI=Body Mass Index; BP=bipolar disorder; C=Comparison; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-M=Clinical Global Impressions Scale-Bipolar-modified (for long-term follow-up); CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-EI=Clinical Global Impressions-Efficacy Index; CGI-I=Clinical Global Impressions Scale, Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSS=Depressive Syndrome Scale; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; IMPS=Inpatient Multidimensional Psychiatric Scale; KAS=Katz Adjustment Scale; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MOS-Cog=Medical Outcomes Study Cognitive Scale; MRS=Mania Rating Scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PGWB=Psychological General Well-being Scale; PMID=PubMed Identification Number; PSQI=Pittsburgh Sleep Quality Index; QIDS-SR=Quick Inventory of Depressive Symptomatology (Self-reported); RCT=randomized controlled trial; ROB=risk of bias; SAS=Simpson Angus Scale; SDS=Sheehan Disability Scale; TMT=Trail Making Test; WPAI=Work Productivity and Activity Impairment Questionnaire; YMRS =Young Mania Rating Scale

Appendix Table 16. Summary risk of bias assessments: other monotherapy

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Long-acting injectable Aripiprazole vs. placebo	Calabrese, 2017 ⁸ Industry 28146613	Moderate	Allocation concealment unclear. Differential attrition between arms. 61.7% attrition rate, 29% not due to relapse. Sensitivity testing for informative withdrawal
Aripiprazole vs. placebo	Keck, 2006 ⁹ Industry 16669728	Moderate	Randomization not described. Allocation concealment not described. Blinding of patients, providers, outcome assessors not described. Attrition 58% and differential drop-out.
Olanzapine vs. placebo	Tohen, 2006 ¹⁹ Industry 16449478	Moderate	Differential withdrawal rates (32% olan, 13% plac) and high dropout of olanzapine group may bias results.
Olanzapine vs. placebo vs. risperidone	Vieta, 2012 ²³ Industry 22503488	High	High - blinding and randomization procedures not well described. Period II results are biased by the drug assignment being open label. Period three efficacy scores are likely to be biased by the large attrition rate.
Risperidone vs. placebo	Quiroz, 2010 ²² Industry 20227682	Moderate (High for log-rank test)	Randomization and blinding well described. Nonrelapse withdrawal 26%.
Lamotrigine vs. Lithium vs. placebo	Bowden, 2003 ⁴ Industry 12695317	Moderate (High for log rank test)	Randomization and blinding procedures not described. Balanced traits among groups at baseline. Efficacy data may be biased by dropout as endpoints are LOCF and differential nonrelapse dropout rates that range from 16-25% of patients for each arm.
	Calabrese, 2003 ⁵ Industry 14628976	Moderate (High for log rank test)	Randomization and allocation concealment not described. Balanced traits among groups at baseline. Efficacy data may be biased by dropout as endpoints are LOCF. 34% withdrawal.
Lamotrigine vs. placebo (rapid cyclers)	Calabrese, 2000 ¹⁷ Industry 11105737	Moderate (High for log rank test)	Randomization and allocation concealment not described. Balanced traits among groups at baseline. ITT using LOCF. Log rank test. 67% attrition, 15% nont related to relapse.
Fluoxetine vs. lithium vs. placebo	Amsterdam, 2010 ³ Government/Non profit 20360317	Moderate	Randomization may not have been successful as it relates to a person's likelihood of relapse; randomization, allocation, and blinding procedures are underdescribed. 23% dropout.
Divalproex vs. lithium (rapid cyclers)	Calabrese, 2005 ¹⁶ Government 16263857	Moderate (High for log rank test)	Randomization and allocation not described. Balanced traits among groups at baseline. ITT. Log rank test. 25% nonrelapse attrition

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Divalproex vs. lithium vs. placebo	Bowden, 2000 ¹ Industry 10807488 12784116 ²	High	Appears to be unblinded. Randomization not described. Nonrelapse dropout of 40%.
Carbamazepine vs. lithium	Hartong, 2003 ¹⁰ Industry/Government 12633122	Low	No sources of bias identified.
	Greil, 1997 ¹¹ Government 9165384 9864077 ¹² 10529070 ¹³ 10529071 ¹⁴ 11093063 ¹⁵	High	Study is unblinded, there may be underlying differences between the groups in their likelihood to recur because of differences baseline disease history. Dropout is inconsistent between groups and no explanation is provided for why patients dropped.
Lithium + valproate vs. valproate vs. lithium	Balance Investigators, 2010 ¹⁸ Industry 20092882	Moderate	Open label. Intention To Treat used, but handling of dropouts/missing data not described.
Olanzapine vs. divalproex	Tohen, 2003 ²⁰ Industry 12832240 Extension of Tohen, 2002b ²¹ 12042191	High	Randomization and blinding procedures not described. Log rank test. Attrition 84%, unclear nonrelapse withdrawal.
Olanzapine vs. lithium	Tohen, 2005 ²⁴ Industry 15994710	High	Well-constructed and reported study with high attrition rate (61%). Time to recurrence only includable outcome (log rank test).
Lamotrigine vs. discontinue mood stabilizers	Newport, 2008 ²⁷ Gov't + nonprofit 18402631	High	Patients chose treatment assignment. Initial differences at baseline are noted.
Venlafaxine vs. placebo	Amsterdam, 2015 ²⁶ Government 26143402	High (RCT extension of responders)	RCT extension. Did report baseline at maintenance phase; appeared balanced on measured variables. 43% loss from initial randomization, further 18% at maintenance

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Paliperidone vs. placebo vs. olanzapine	Berwaerts, 2012 ²⁵ Industry 22377512	High (RCT Extension)	Large dropout rate among all study arms, across all time periods Did report baseline at maintenance phase.
Quetiapine vs. lithium vs. placebo + lithium	Weisler, 2011 ⁷ Industry 22054050	Moderate	Generally a well conducted and reported study, however some sources of bias present related to dropout rates. Overall 21% withdraw due to reasons unrelated to recurrence; however by week 16 more than 50% of the placebo group has dropped for all causes, as well as 40% of the lithium group and 25% of the quetiapine group)

Abbreviations: BP=bipolar; LOCF=Last observation carried forward; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table 17. Outcomes summary: other monotherapy versus placebo for maintenance

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Long-acting injectable Aripiprazole vs. placebo	Calabrese, 2017 ⁸	<p><u>Time to any recurrence</u> 52 weeks HR 0.45 (95% CI 0.30, 0.68) Favors Aripiprazole</p> <p><u>Any relapse</u> 52 weeks Aripiprazole 35/132 Placebo 68/133 Favors Aripiprazole p<0.0001</p> <p><u>Manic relapse</u> 52 weeks Favors Aripiprazole p<0.0001</p> <p><u>Depression relapse</u> 52 weeks NS</p>	NA (Exclude for attrition = 62%)	NR	<u>Weight gain > 7%</u> Aripiprazole 23/132 Placebo 17/133	<p><u>SAE >1 patient</u> Aripiprazole 0.8% Placebo 2.3%</p> <p>1 death reported</p> <p><u>EPS</u> Aripiprazole 36/132 Placebo 22/133</p>
Aripiprazole vs. placebo	Keck, 2006 ⁹ 16669728	<p><u>Time to relapse</u> 26 weeks HR 0.52 (95% CI 0.30, 0.91) Favors Aripiprazole</p> <p><u>Time to manic relapse</u> 26 weeks HR 0.31 (95% CI 0.12, 0.77) Favors Aripiprazole</p> <p><u>Time to depression relapse</u> 26 weeks NS</p>	NA (Exclude for attrition = 58%)	NA (Exclude for attrition = 58%)	NR	<p>1 placebo group patient attempted suicide</p> <p>EPS "more frequently in the aripiprazole group"</p> <p>7% Weight gain Aripiprazole 13% Placebo 0%</p>

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Divalproex vs. placebo	Bowden, 2000 ¹ 10807488 12784116 ²	Time to any recurrence 12 months NS Time to mania recurrence 12 months NS Time to depression recurrence 12 months NS	NA (Exclude for attrition = 69%)	NR	NR	SAE NR Tremor Divalproex 41% (77/187) Placebo 13% (12/94) Favors Placebo p<0.001 Akathisia Divalproex <1% (1/187) Placebo 1% (1/94) NS
Fluoxetine vs. placebo	Amsterdam, 2010 ³ 20360317	<u>Time to Relapse to Depression</u> 50 week Log rank Favors Fluoxetine p=0.03	NA (Exclude for attrition = 72%)	NR	NR	SAE No Events Akathisia Fluoxetine 1 event/28 patients
Lamotrigine vs. placebo	Bowden, 2003 ⁴ 12695317	<u>Time to any recurrence</u> 18 months Log rank Favors Lamotrigine p=0.02 <u>Time to mania recurrence</u> 18 months Log rank NS <u>Time to depression recurrence</u> 18 months Log rank Favors Lamotrigine p=0.002	NA (Exclude for attrition = 80%)	NA	NA	SAE 1 lamotrigine patient hospitalized for rash 1 lamotrigine patient attempted suicide Suicidality per HAM-D NS between groups

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
	Calabrese, 2003 ⁵ 14628976	<u>Time to any recurrence</u> 18 months Log rank Favors Lamotrigine p=0.03 <u>Time to mania recurrence</u> 18 months Log rank NS <u>Time to depression recurrence</u> 18 months Log rank Favors Lamotrigine p=0.047	NA (Exclude for attrition = 85%)	NA	NA	<u>SAE</u> 1 death in lamotrigine groups Suicidality per HAM-D NS between groups Tremor Lamotrigine 5% (9/169) Placebo 5% (6/121) Lamotrigine vs. Placebo NS
Lamotrigine vs. placebo (rapid cyclers)	Calabrese, 2000 ¹⁷ Industry 11105737	<u>Time to new drug</u> 26 weeks Log rank No difference by group, or stratified by bipolar type	NA (Exclude for attrition = 68%)	NA	<u>Time to overall withdrawal</u> No difference by group. BPII Lamotrigine group more like remain in study p=0.015	<u>SAE</u> Lamotrigine: 1 tachycardia Placebo: 1 basal cell carcinoma, 1benign skull tumor None reporte related to treatment
Lamotrigine vs. discontinued mood stabilizers	Newport, 2008 ²⁷ 18402631	<u>Relapse</u> 40 weeks Lamotrigine 3/10 Discontinued 16/16 Favors Lamotrigine	NR	NR	NR	NR

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Olanzapine vs. placebo	Tohen, 2006 ¹⁹ Moderate 16449478	<u>Time to Relapse, Any Mood Episode (Median)</u> 48 weeks Favors Olanzapine HR 2.67 (95% CI 2.03, 3.50), p<0.001 <u>Time to relapse, Mania (25th percentile)</u> Favors Olanzapine HR 3.90 (95% CI 2.40, 6.33), p<0.001 <u>Time to relapse, depression (25th percentile)</u> Favors Olanzapine HR 2.10, (95% CI 1.46, 3.02), p<0.001	<u>NA</u> (Exclude for attrition = 84%)	NA	NA	<u>SAE</u> Olanzapine 3% (7/225) Placebo 7% (10/136) NS <u>EPS</u> Parkinsonism Olanzapine 2% (5/206) Placebo 0% (0/118) Favors Placebo Absolute Risk Reduction 0.02 (95% CI 0.003, 0.045) <u>Akathisia</u> Olanzapine 5% (9/194) Placebo 1% (1/119) NS <u>Dyskinesia</u> Olanzapine 0% (0/216) Placebo 1% (1/133) NS
	Vieta, 2012 ²³ 22503488	<u>Time to first recurrence of mood symptoms</u> 18 months Log-rank (by region) Favors Olanzapine p<0.001	<u>NA</u> (Due to attrition =58%)	NA (Due to attrition =58%)	NR	Reported no SAE in period III (maintenance phase)

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
	Berwaerts, 2012 ²⁵ 22377512	<u>Time to Relapse to Any Mood Episode</u> Favors Olanzapine Post hoc p<0.001 (YMRS≥15, CGI-BP-S for mania≥4; OR YMRS<15, MADRS≥16 and CGI-BP-S for depression≥4; hospitalization; therapeutic intervention or other clinically relevant indicators) Paliperidone Mean 558 days; Placebo Mean 283 days <u>Time to Relapse to Manic Episode</u> Favors Olanzapine Post hoc p<0.001	<u>NR</u>	NR	<u>Death</u> none <u>Withdrawal for AE</u> Paliperidone 5 (3%) Placebo 4 (3%) <u>Withdrawal for Nonresponse</u> Paliperidone 1 (1%) Placebo 2 (1%)	<u>SAE</u> up to 3 years Olanzapine 10% Placebo 22% <u>EPS</u> up to 3 years Olanzapine 1% Placebo 1%

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Paliperidone vs. placebo	Berwaerts, 2012 ²⁵ 22377512	<p><u>Time to Relapse to Any Mood Episode</u> Favors Paliperidone HR 1.43 (95% CI 1.03,1.98) p=0.017 (YMRS≥15, CGI-BP-S for mania≥4; OR YMRS<15, MADRS≥16 and CGI-BP-S for depression≥4; hospitalization; therapeutic intervention or other clinically relevant indicators) Paliperidone Mean 558 days; Placebo Mean 283 days</p> <p><u>Time to Relapse to Manic Episode</u> Favors Paliperidone HR 2.06 (95% CI 1.32,3.22) p<0.001 Paliperidone Mean 558 days; Placebo Mean 283 days</p>	<p><u>YMRS Change</u> up to 3 years Favors Paliperidone LSM difference -4.5 (95% CI -6.92, -1.98)</p> <p><u>MADRS Change</u> up to 3 years NS LSM difference 0.3 (95% CI -1.87,2.55)</p>	NR	<p><u>Death</u> up to 3 years Paliperidone 2 (pneumonia, overdose) Placebo 0</p> <p><u>Withdrawal for AE</u> Olanzapine 7/83 (8%) Placebo 4/148 (3%)</p> <p><u>Withdrawal for Nonresponse</u> Olanzapine 0/83 (1%) Placebo 2 /148(1%)</p>	<p><u>SAE</u> up to 3 years Paliperidone 11% Placebo 22%</p> <p><u>EPS</u> up to 3 years Paliperidone 1% Placebo 1%</p>

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Quetiapine vs. placebo	Weisler, 2011 ⁷ 22054050	Time to recurrence of any mood event Favors Quetiapine HR 0.29 (95% CI 0.23, 0.38), p<0.0001 Time to recurrence of manic event Favors Quetiapine HR 0.29 (95% CI 0.21, 0.40), p<0.0001 Time to recurrence of depression symptoms Favors Quetiapine HR 0.30 (95% CI 0.20, 0.44), p<0.0001	<u>NA</u> (Exclude for attrition 55%)	NR	<u>NR</u>	<u>SAE</u> 5 quetiapine 11 placebo <u>EPS</u> 16 quetiapine 18 placebo No deaths
Risperidone vs. placebo	Quiroz, 2010 ²² 20227682	<u>Time to first recurrence of mood symptoms</u> 24 months Log-rank test Favors Risperidone HR 0.40 (95% CI 0.27, 0.59) p=0.001	<u>NA</u> (Exclude for attrition =64%)	NA	<u>Time to withdrawal for any reason</u> 24 months Log-rank test Favors Risperidone HR 0.49 (95% CI 0.36, 0.67) p=0.001	<u>SAE</u> 1 diabetes mellitus in Risperidone group <u>EPS</u> 3%both groups
	Vieta, 2012 ²³ 22503488	<u>Time to first recurrence of mood symptoms</u> 18 months Log-rank (by region) Favors Risperidone p=0.03	<u>NA</u> (Exclude for attrition =58%)	NA	<u>NR</u>	Reported no SAE in period III (maintenance phase)

Abbreviations: AE=Adverse Events; CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CI=Confidence Interval; EPS=extrapyramidal symptoms; HAM-D=Hamilton Scale for Depression; HR=Hazard Ratio; LSM=least-squares means; MADRS=Montgomery-Asberg Depression Rating Scale; NA=Not applicable; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table 18. Strength of evidence assessment: other monotherapy versus placebo for maintenance

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Long-acting injectable Aripiprazole vs. placebo	Time to relapse 52 wks Relapse 52 wks	1 RCT (n=266)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Aripiprazole vs. placebo	Time to Relapse 26 wks	1 RCT (n=161)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Divalproex vs. placebo	Time to relapse 52 wks	1 RCT (n=281)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Fluoxetine vs. placebo	Time to relapse to depression 50 wks	1 RCT (n=55)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Lamotrigine vs. placebo	Time to relapse 18 mths	2 RCT (n=471)	See table above	High (log rank tests)	Consistent	Direct	Imprecise	Insufficient
Lamotrigine vs. placebo (rapid cyclers)	Time to new drug treatment	1 RCT (n=182)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Lamotrigine vs. discontinue mood stabilizers	Relapse 40 wks	1 Observational (n=26)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. placebo	Time to relapse 18 mths to 3 yrs	3 RCT (n=855)	18 months to 3 years	High	Consistent	Direct	Imprecise	Insufficient
Paliperidone vs. placebo	Time to Relapse 3 yrs YMRS 3 yrs MADRS	1 RCT extension (n=300)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Quetiapine vs. placebo	Time to relapse 104 wks	1 RCT (n=808)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Risperidone vs. placebo	Time to relapse 52 wks	2 RCT (n=353)	See table above	High (log rank test)	Consistent	Direct	Imprecise	Insufficient

Abbreviations: MADRS=Montgomery-Asberg Depression Rating Scale; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Appendix Table I9. Outcomes summary: other monotherapy versus active control for maintenance

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Carbamazepine vs. lithium	Hartong, 2003 ¹⁰ 12633122	<u>Time to relapse</u> Proportional hazard assumption did not hold	NR	NR	NR	<u>SAE</u> <u>NR</u>
	Greil, 1999 10529070 ¹³ 10529071 ¹⁴	<u>Time to clinical or subclinical recurrence BP-I</u> 2.5 years Favors lithium p=0.034 n=114 <u>Time to clinical or subclinical recurrence BP-II or NOS</u> 2.5 years NS n=57	NR	NR	NR	1 suicide, 1 attempted suicide in carbamazepine group
Divalproex vs. lithium (rapid cyclers)	Calabrese, 2005 ¹⁶ Government 16263857	<u>Time to treatment for mood episode, depression treatment, elevated mood treatment</u> 26 weeks No differences between groups	NA (attrition 88%)	NA	<u>Time to overall withdrawal</u> 26 weeks No difference between groups	<u>SAE</u> NR Tremors/polyuria/polydipsia "more common in those assigned to lithium"
Paliperidone vs. olanzapine	Berwaerts, 2012 ²⁵ 22377512	<u>No usable outcomes</u>				

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Fluoxetine vs. Lithium	Amsterdam, 2010 ³ 20360317	<u>Time to Relapse to Depression</u> 50 week Favors Fluoxetine p=0.03 <u>Relapse</u> 50 week Favors Fluoxetine HR=0.04 (95%CI 0.2,0.9)	<u>YMRS Change</u> 50 week Fluoxetine -6.3 (95%CI -47.5, 34.9) Lithium 7.2 (95%CI -33.3,53.8)	NR	Withdrawal for AE Fluoxetine 1 Lithium 1	<u>SAE</u> No Events
Lamotrigine vs. Lithium	Bowden, 2003 ⁴ 12695317	<u>Time to any recurrence</u> 18 months Log rank NS <u>Time to mania recurrence</u> 18 months Log rank NS <u>Time to depression recurrence</u> 18 months Log rank NS	NA (Exclude for attrition = 80%)	NA	NA	<u>SAE</u> 1 lamotrigine patient hospitalized for rash 1 lamotrigine patient attempted suicide Suicidality per HAM-D NS between groups

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
	Calabrese, 2003 ⁵ 14628976	<u>Time to any recurrence</u> 18 months Log rank NS <u>Time to mania recurrence</u> 18 months Log rank NS <u>Time to depression recurrence</u> 18 months Log rank NS	NA (Exclude for attrition = 85%)	NA	NA	<u>SAE</u> 1 death in lamotrigine groups Suicidality per HAM-D NS between groups
Lithium vs. valproate	Balance Investigators, 2010 ¹⁸ 20092882	<u>Time to new intervention for emerging mood episode</u> 24 months Hazard ratio Favors Lithium HR 0.71 (0.51,1.00) p=0.047	NR	GAF NS	EuroQol (EQ-5D) (quality of life) NS Overall Withdrawal Lithium: 23/110 Valproate: 23/110 Withdrawal lack of efficacy NR Withdrawal adverse events Lithium: 6/110 Valproate: 4/110	<u>SAE</u> NS Valproate: 7 SAE including 3 deaths Lithium: 5 SAE including 2 deaths

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium vs. divalproex	Bowden, 2000 ¹ 10807488 12784116 ²	<u>Time to any recurrence</u> 12 months NS <u>Time to mania recurrence</u> 12 months NS <u>Time to depression recurrence</u> 12 months NS	NA (Exclude for attrition = 69%)	NR	NR	<u>SAE</u> NR <u>Tremor</u> Divalproex 41% (77/187) Lithium 42% (38/94) Divalproex vs. Lithium NS <u>Akathisia</u> Divalproex <1% (1/187) Lithium 4% (4/94) Divalproex vs. Lithium Favors divalproex p=0.04
Olanzapine vs. divalproex	Tohen, 2003 ²⁰ Industry 12832240 Extension of Tohen, 2002b ²¹ 12042191	<u>Time to relapse</u> 42 weeks Log rank NS	NA (attrition 84%)	NA	NR	SAE not reported
Olanzapine vs. Lithium	Tohen, 2005 ²⁴ High 15994710	<u>Time to Relapse (YMRS and/or HAM-D>15)</u> 52 weeks Log rank NS p=0.07 <u>Time to hospitalization</u> 52 weeks Log rank Favors Olanzapine p=0.01	NA (Exclude for attrition = 61%)	NR	<u>Overall Withdrawal</u> Olanzapine: 116/217 Lithium: 144/214	<u>SAE</u> 2 deaths, lithium, 1 suicide, 1 accident EPS NS

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Quetiapine vs. Lithium	Weisler, 2011 ⁷ 22054050	Time to recurrence of any mood event Favors Quetiapine HR 0.66 (95% CI 0.49, 0.88), p=0.005 Time to recurrence of manic event NS Time to recurrence of depression symptoms Favors Quetiapine HR 0.54 (95% CI 0.35, 0.84), p=0.006	<u>NA</u> (Exclude for attrition 55%)	NR	NR	<u>SAE</u> 5 quetiapine 10 lithium <u>EPS</u> 16 quetiapine 38 lithium No deaths
Venlafaxine vs. Lithium	Amsterdam, 2015 ²⁶ 26143402	<u>Time to depression relapse</u> 6 months Log rank NS	<u>YMRS</u> <u>NS</u>	NR	<u>Withdrawal for AE</u> Venlafaxine 1 Lithium 0	NR
Risperidone vs. olanzapine	Vieta, 2012 ²³ 22503488	<u>Time to first recurrence of mood symptoms</u> 18 months Post-hoc Log-rank Favors Olanzapine p=0.001	<u>NA</u> (Due to attrition =58%)	NA (Due to attrition =58%)	NR	Reported no SAE in period III (maintenance phase)

Abbreviations: AE=Adverse Events; BP=bipolar disorder; CI=Confidence Interval; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HR=Hazard Ratio; NA= Not Applicable; NOS=Not Otherwise Specified; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Serious Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table I10. Strength of evidence assessment: other monotherapy versus active control for maintenance

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Carbamazepine vs. Lithium	Time to recurrence 2.5 yrs	1 RCT (Greil 1999) (n=171)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Divalproex vs. lithium (rapid cyclers)	Time to treatment for mood episode 26 weeks	1 RCT (n=60)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Fluoxetine vs. Lithium	Time to relapse to depression 50 wks	1 RCT (n=54)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Lamotrigine vs. Lithium	Time to recurrence 18 mths	2 RCTs (n=390)	See table above	High	Consistent	Direct	Imprecise	Insufficient
Lithium vs. Valproate*	Time to new intervention for emerging mood episode 24 mths EuroQoL 24 mths	1 RCT (n=220)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Lithium vs. divalproex*	Time to recurrence 12 mths	1 RCT (n=372)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. divalproex	Time to recurrence 47 weeks	1 RCT (n=251)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Olanzapine vs. Lithium	Time to relapse 104 wks time to hospitalization 104 wks	1 RCT (n=431)	See table above	High	Consistent	Direct	Imprecise	Insufficient
Quetiapine vs. Lithium	Time to relapse 104 wks	1 RCT (n=768)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Paliperidone vs. Olanzapine	No usable outcomes 3 yrs	1 RCT extension (n=235)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Venlafaxine vs. Lithium	Time to Relapse 6 mths YMRS 6 mths	1 RCT extension (n=55)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Risperidone vs. Olanzapine	Time to relapse 18 mths	1 RCT (n=263)	See table above	High	Unknown	Direct	Imprecise	Insufficient

* If aggregating across lithium versus divalproex or valproate, strength of evidence remains insufficient due to inconsistency between study findings.

Abbreviations: RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

Section 3. Combination Therapy

Appendix Table I11. Characteristics of eligible studies: combination therapy for maintenance

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Balance Investigators, 2010 ¹⁸ RCT Multisite US and Europe Industry RoB Moderate 20092882	N=330 Mean Age 43 Female 49% Race NR BP I 100% Outpatient	Not having acute episode; Not defined Pregnant/Nursing	Lithium 0.4-1.0 mmol/L mean NR + Valproate 750-1250 or highest tolerated mean NR n=110	C1: Lithium 0.4-1.0 mmol/L mean NR N=110 C2: Valproate 750-1250 or highest tolerated mean NR n=110	24 months	GAF EuroQol (EQ-5D) (quality of life) Relapse Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Marcus, 2011 ²⁸ RCT Multisite/Not Disclosed (8 countries) Industry RoB High 21443567	N = 337 Mean Age 39 Female 55% White 68% BP I 100% Outpatient	Manic/Mixed; YMRS \geq 16 at study entry; Current episode <2 years; YMRS \leq 12, MADRS \leq 12 at randomization after 12 weeks of stabilization treatment First manic episode Schizoaffective Substance abuse Other mental health Neurological disorders Taking other meds Labs/other conditions	Aripiprazole 10-30 mg/day (15.8-16.9 mg/day) + Lithium or valproic acid	Placebo + Lithium or valproic acid	52 weeks	YMRS MADRS CGI-BP-S Relapse Adverse Events EPS Withdrawal 43%
Carlson, 2012 ²⁹ RCT of responders Multisite US Industry RoB High 22329471	N=351 Mean Age 39 Female 65% White 90% BP I 100% Outpatient	Randomization after stabilization; 8 weeks at YMRS \leq 12, MADRS \leq 12. Study entry manic or mixed YMRS \geq 16 in previous 3 months with or without rapid cycling (4 to 7 mood episodes per year) Substance abuse Other Mental Health Conditions Pregnant/Nursing Labs/other conditions First manic episode Treatment refractory mania/mixed mania	Aripiprazole target 15 mg/day (range 10-30 mg/day) +Lamotrigine target 200 mg/day (range 100-200 mg/day)	Placebo +Lamotrigine target 200 mg/day (range 100-200 mg/day)	52 weeks	Time to relapse (hospitalization; SAE or lack of effect, including YMRS>14 and MADRS \leq 16 manic or YMRS \leq 14 and MADRS >16) YMRS MADRS CGI-BP Withdrawal 66% (Time to recurrence outcomes only included) Nonrelapse withdrawal ~40%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Woo, 2011 ³⁰ RCT Multisite/Asia Industry RoB High 22134973	N = 83 Mean Age 38 Female 68% White NR Japanese (32%) Korean/Chinese (43%) Other (25%) BP I 100% Outpatient	Manic/Mixed initially with YMRS \geq 20 at study entry; then YMRS \leq 12, MADRS \leq 13 at randomization after 6 weeks of stabilization treatment Schizoaffective Substance abuse Neurological disorders Taking other meds Pregnant/nursing Labs/other conditions	Aripiprazole 10-30 mg/day (17.9 mg/day) + Lithium or valproic acid	Placebo + Lithium or valproic acid	24 weeks	YMRS MADRS CGI-BP-S Relapse Adverse Events EPS Withdrawal 42%
Kemp, 2009 ³¹ RCT of responders Single site US Gov't RoB High 19192457	N=31 Mean Age 36 Female 36% White 82% BP I 75% BP II 25% Outpatient	Stable responders (HAM-D score \leq 20, YMRS score \leq 12.5) Rapid cycling, substance use disorder as ascertained by structured interview; mood episode in previous 3 months Labs/other conditions Pregnant/nursing	Divalproate 250 mg/day (target blood level 50mg/day+ Lithium	Placebo + Lithium	26 weeks	Time to treat mood episode Efficacy YMRS HAM-D GAS Withdrawal 74% (Time to recurrence outcomes only included) Nonrelapse withdrawal 19%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Tohen, 2004 ³² RCT of Responders Multisite US Industry ROB High 15056579 extension of Tohen, 2002 ³³ 11779284	N = 99 Mean Age 41 Female 48% White 85% BP-I 100% Outpatient	Responders to olanzapine + lithium or valproate mania and depression no worse than mild; First Manic Episode Labs/Other Conditions	Olanzapine 10 mg/day with flexible dosing from 5-20 mg/day Adjunctive to ongoing open-label valproate or lithium n=51	Placebo Adjunctive to ongoing open- label valproate or lithium n=48	18 months	Time to any mood episode; Withdrawal 78% (Time to recurrence outcomes only included) Unclear nonrelapse withdrawal
Suppes, 2009 ³⁴ RCT Multisite US/Canada Industry RoB High 19289454	N = 623 Mean Age 40 Female 53% White 82% BP I 100% Inpatient	Mania at entry; Stable at randomization after Lithium or Valproate; YMRS and MADRS \leq 12 AND at least 1 mood episode of any type in past 2 years and another 6 months prior to randomization First Manic Episode Substance Abuse Other Mental Health Conditions Pregnant/Nursing	Quetiapine 400-800 mg/day (519 mg/day mean) + Valproate 50-125 mcg/mL target OR Lithium 0.5-1.2 mEq/L target	Placebo + Valproate 50-125 mcg/mL target OR Lithium 0.5-1.2 mEq/L target	104 weeks (only time to occurrence and withdrawals used due to attrition)	Recurrence Adverse Events Withdrawal 71% (Time to recurrence outcomes only included) Nonrelapse withdrawal 35%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Vieta, 2008 ³⁵ RCT Multisite 4 Continents Industry RoB 18579216	N = 706 Mean Age 42 Female 55% White 97% BP I 100% Inpatient (1 week) Outpatient (2-6 weeks, subject to inspector discretion)	Mania, Depression, Mixed; latest episode of any type within 26 weeks, achieved clinical stability (YMRS and MADRS \leq 12) prior to randomization, subject to specified time periods Substance Abuse; Other Mental Health Conditions; Taking Other Meds; Pregnant/Nursing	Quetiapine 400-800 mg/day (497 mg/day mean) + Valproate 50-125 mcg/mL target OR Lithium 0.5-1.2 mEq/L target	Placebo + Valproate 50-125 mcg/mL target OR Lithium 0.5-1.2 mEq/L target	104 weeks (only time to occurrence and withdrawals used due to attrition)	Recurrence CGI-BP PANSS-P SDS PGWB SAS BARS AIMS Withdrawal 51% (Time to recurrence outcomes only included) Nonrelapse withdrawal 16%
Bobo, 2011 ³⁶ RCT Single-site US Industry RoB High 22104634	N = 50 Mean Age 40 Female 67% White 67% BP I 73% BP II 27% Outpatient	Any Phase Schizoaffective; Other Mental Health Conditions; Pregnant/Nursing	Risperidone long- acting injectable 27 \pm 10.4 mg every 2 weeks + Treatment as Usual	No Placebo + Treatment as Usual	52 weeks	AIMS BARS CGI-S MADRS Quick Inventory of depressive symptoms self-report (QIDS-SR) SAS YMRS Withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Macfadden, 2009 ³⁷ RCT Multisite 2 Continents Industry RoB High 19922552	N = 124 Mean Age 39 Female 28% White 10% BP I 100% Inpatient and outpatient	Any Phase including euthymic; 4 or more mood episodes in past year Substance Abuse; Other Mental Health Conditions; Taking other Medications; Abnormal Lab Results	Risperidone long- acting injectable 25-30 mg every 2 weeks +Treatment as Usual	Placebo + Treatment As Usual	52 weeks	CGI-BP-C CGI-BP-S MADRS Relapse – Time to (DSM diagnosis for acute mood episode + other complicated criteria) YMRS Withdrawal 48%
Bowden, 2010 ³⁸ RCT of responders Multisite 3 Continents Industry RoB High 20122373 (also 22999893)	N = 240 Mean Age 39 Female 54% White 62% BP I 100% Outpatient	Mania; Initial inclusion: YMRS ≥ 14 with score ≥ 2 on at least four items at screening and admission. Extension inclusion: stabilized (CGI-I ≤ 3 at least 2 consecutive weeks Substance Abuse; Other Mental Health Condition; Pregnant/Nursing; Labs/Other Conditions	Ziprasidone (80-160 mg/day) + Lithium (0.6-1.2 mEq/L) or Valproate (50-125 mcg/mL)	Placebo+ Lithium (0.6-1.2 mEq/L) or Valproate (50-125 mcg/mL)	26 weeks	BMI or Weight MADRS Mania Rating Scale (MRS) Relapse – Relative Risk of Relapse - Time to intervention for mood episode Withdrawal 42%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Vieta, 2008 ³⁹ RCT Multisite Spain Industry RoB Moderate 18346292	N = 55 Mean Age 44 Female 65% White NR BP I 76% BP II 24% Outpatient	Euthymic; YMRS≤12; MADRS≤20; 2+ episodes in past year; ≥6 months in remission; Being treated with Lithium (≥0.6 meq/L) Substance Abuse; Other Mental Health Conditions; Taking Other Meds; Pregnant/Nursing	Oxcarbazepine 1200 mg/day+ Lithium 300-1200 mg/d (mean NR)	Placebo + Lithium 300-1200 mg/d (mean NR)	52 weeks	Relapse (DSM-IV criteria for manic, hypomanic, mixed or depressive episode; OR YMRS≥12; OR MADRS≥20) CGI-BP-M GAF BIS-11 Withdrawal 36%
Vieta, 2006 ⁴⁰ RCT Multisite Spain Industry RoB High 16649836	N = 25 Mean Age 49 Female 72% White NR BP I 76% BP II 24% Outpatient	Euthymic; CGI-BP-M ≥4; HAMD≤8 YMRS≤4; Treated with lithium for 6 weeks; Last episode within 6 mos; Substance abuse Pregnant/nursing Labs/other conditions	Gabapentin 300-800 mg/tid (400mg/tid) + Lithium and/or Valproate and/or Carbamazepine NR	Placebo + Lithium and/or Valproate and/or Carbamazepine NR	52 week	CGI-BP-M YMRS HAM-D PQSI Time to Relapse Withdrawal 48%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Zarate, 2004 ⁴¹ Single-Site RCT US Gov't+nonprofit RoB High 14702269	N = 37 Mean Age 34 Female 78% White NR BP I 100% Setting NR	Manic /Mixed at study entry; DSM-IV criteria (Structured Clinical Interview) Euthymic by randomization (week 10); YMRS≤10; HAM-D≤10 Schizoaffective Substance abuse Other mental health Labs/other conditions	Perphenazine 4-64 mg/day + (Mood Stabilizers Lithium 0.6-1.2 meq/L And/Or Carbamazepine 4- 12 mg/L And/Or Valproate 50-125 mg/L)	Placebo+ (Mood Stabilizers Lithium 0.6-1.2 meq/L And/Or Carbamazepine 4-12 mg/L And/Or Valproate 50- 125 mg/L)	6 months	Relapse (Not Defined) HAM-D Withdrawal 35%
Nierenberg, 2016 ⁴² RCT Multisite US Government RoB High 26845264	N=482 Mean Age 39 Female 59% White 72% BP I 68% BP II, NOS NR Outpatient	Any status Pregnant/Nursing; Labs/Other Conditions	Quetiapine 150-900 mg/day (345 mg/day) + Adjunctive personalized treatment Texas Medication Algorithm	Lithium 0.6-1.2 mEq/L (0.6 mEq/L) + Adjunctive personalized treatment Texas Medication Algorithm	24 weeks	CGI-EI MADRS YMRS Columbia-Suicide Severity Rating Scale Withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	# Randomized Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Dosage	Comparison Dosage	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Vieta, 2010 ⁴³ Observational (Partial responders of earlier RCT) Multisite Not Disclosed Industry RoB High 20429835 (Continuation of 18381903)	N = 283 Mean Age 43 Female 53% White 93% BP I 100% Outpatient	Mania; Mania Rating Scale (Spitzer, 1978) ≥ 14 with score ≥ 2 on four items at screening and admission Other Mental Health Conditions; Substance Abuse	Valproate 500-2500 mg/day (1174.3 mg/day average - last 4 weeks) + Aripiprazole 15-30 mg/day (17.1- 18.5 mg/day average)	Lithium 500-1500 mg/day (1105.5 mg/day average) + Aripiprazole 15-30 mg/day (16.9-18.4 mg/day average)	46 weeks	BMI or Weight LIFE-RIFT MADRS Relapse - Emergent Depression Incidence (MADRS total score >= 18 and >= 4 point increase in two consecutive assessments or last observation) Relapse (YMRS total score <=12 and MADRS total <=8 of patients who achieved remission at end of week 6) YMRS Withdraw 48%

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Scale; BIS-11=Barratt Impulsiveness Scale; BMI=Body Mass Index; BP=bipolar disorder; C=Comparison; CGI-BP=Clinical Global Impressions Scale for Bipolar Disorder; CGI-BP-M=Clinical Global Impressions Scale-Bipolar-modified (for long-term follow-up); CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-EI=Clinical Global Impressions-Efficacy Index; CGI-I=Clinical Global Impressions Scale, Improvement; CGI-S=Clinical Global Impressions, Severity Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSS=Depressive Syndrome Scale; EPS=extrapyramidal symptoms; ESRS=Extrapyramidal Symptom Rating Scale; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; IMPS=Inpatient Multidimensional Psychiatric Scale; KAS=Katz Adjustment Scale; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; MOS-Cog=Medical Outcomes Study Cognitive Scale; MRS=Mania Rating Scale; NOS=not otherwise specified; NR=not reported; PANSS=Positive and Negative Syndrome Scale; PGWB=Psychological General Well-being Scale; PMID=PubMed Identification Number; PSQI=Pittsburgh Sleep Quality Index; QIDS-SR=Quick Inventory of Depressive Symptomatology (Self-reported); RCT=randomized controlled trial; ROB=risk of bias; SAS=Simpson Angus Scale; SDS=Sheehan Disability Scale; TMT=Trail Making Test; WPAI=Work Productivity and Activity Impairment Questionnaire; YMRS =Young Mania Rating Scale

Appendix Table I12. Summary risk of bias assessments: combination therapy for maintenance

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Lithium + valproate vs. valproate vs. lithium	Balance Investigators, 2010 ¹⁸ Industry 20092882	Moderate	Open label. Intention To Treat used, but handling of dropouts/missing data not described.
Aripiprazole + mood stabilizer vs. placebo + mood stabilizer	Marcus, 2011 ²⁸ Industry 21443567	High	High Withdrawal rate (43%) - maintenance study; blinding procedures not disclosed.
	Carlson, 2012 ²⁹ Industry 22329471	High	High nonrelapse withdrawal rate (40%). Overall attrition 66%. Randomization, concealment, and blinding not described.
	Woo, 2011 ³⁰ Industry 22134973	High	High Withdrawal rate (42%) – maintenance study; Randomization and blinding procedures not disclosed.
Divalproex + lithium vs. placebo + lithium alone	Kemp, 2009 ³¹ Government 19192457	High	Randomization and allocation not reported. Overall 19% withdraw due other than relapse.
Quetiapine + mood stabilizers vs. placebo + mood stabilizers	Suppes, 2009 ³⁴ Industry 19289454	High	Blinding not described; differential dropout rates. High drop-out rates overall.
	Vieta, 2008 ³⁵ Industry 18579216	High	Generally well reported with minor concerns related to blinding, subjective definition of recurrence. High drop-out rates overall.
Risperidone long-acting injectable+ treatment as usual vs. placebo + treatment as usual	Macfadden, 2009 ³⁷ Industry 19922552	High	BPII patients enrolled, but removed from analysis. 48% dropout overall. Large differential dropout with 58% placebo and 40% of treatment groups dropping.
Risperidone long-acting injectable+ treatment as usual vs. treatment as usual	Bobo, 2011 ³⁶ Industry 22104634	High	No blinding. Treatment As Usual not well controlled. Treatment regimes of the two groups prior to study were not tested for similarity and appear as though they may differ statistically. Results may be due to differences in TAU. 25% dropout.

Drug	Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Olanzapine + mood stabilizer vs. placebo + mood stabilizer	Tohen, 2004 ³² Industry 15056579 extension of Tohen, 2002 ³³ 11779284	Moderate (High for log rank)	Allocation concealment not described. Log rank test. Unclear nonrelapse withdrawal.
Oxcarbazepine lithium vs. placebo + lithium	Vieta, 2008 ³⁹ Industry 18346292	Moderate	Patients, staff, and raters may not be blinded; procedures not described
Gabapentin + mood stabilizers vs. placebo + mood stabilizers	Vieta, 2006 ⁴⁰ Industry 16649836	High	Distribution of BP I and BP II patients differs between treatment arms, creating a residual confounder.
Perphenazine + mood stabilizers placebo + mood stabilizers	Zarate, 2004 ⁴¹ Gov't+nonprofit 14702269	High	Randomization and blinding procedures not disclosed; numerical results of several measured outcomes not presented; Relapse not defined
Ziprasidone + mood stabilizers vs. placebo + mood stabilizers	Bowden, 2010 ³⁸ Industry 20122373 (also 22999893)	High	Randomization and blinding procedures not described. 40%+ dropout.
Quetiapine + personalize treatment vs. Lithium + personalized treatment	Nierenberg, 2016 ⁴² Government 26845264	High	Does not report on adjunctive treatments received in results. Includes those who have 'off-procedure' treatment deviations in analysis, who are people that have taken antipsychotics. Also included are the roughly 30% of people in both treatment arms who have no adjunctive treatment. None of these is accounted for in analysis as a possible confounding influence on the underlying comparison of Quetiapine and Lithium.
Valproic acid + Aripiprazole vs. Lithium + Aripiprazole	Vieta, 2010 ⁴³ Industry 20429835 (Continuation of 18381903)	High	Non-Randomized continuation study of partial responders, no blinding, initial baseline measures of this group may not be similar, appears to be underpowered for the subgroup analysis that is presented. 48% dropout.

Abbreviations: BP=bipolar; LOCF=Last observation carried forward; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table I13. Outcomes summary: combination therapy versus placebo for maintenance

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
Aripiprazole + mood stabilizer vs. placebo + mood stabilizer	Marcus, ²⁸ 2011 High 21443567	Time to Relapse 52 weeks Hazard Ratio 0.54 (0.33, 0.89) Favors Aripiprazole	YMRS 52 weeks Mean change Aripiprazole: -0.1 Placebo: 2.9 p<0.001 Favors Aripiprazole MADRS 52 weeks Mean change Aripiprazole: 1.5 Placebo: 2.5 p=0.02 Favors Aripiprazole	CGI-BP-S 52 weeks Ari n=162 Plc n=164 Mean change difference -0.3 (-0.62, -0.07) Favors Aripiprazole Less than MID=1	<u>Weight gain >7%</u> NS <u>Overall Withdrawal</u> Aripiprazole 65/168 (38.7%) Placebo 80/169 (47.3%) NS <u>Withdrawal lack of efficacy</u> Aripiprazole 6/168 (8.3%) Placebo 31/169 (18.3%) p=0.007 <u>Withdrawal for AE</u> Aripiprazole 19/168 11.3% Placebo 15/169 (8.9%) NS	2 deaths, 1 in each arm; 1 suicide day 83 deemed not due to treatment 1 tardive dyskinesia (placebo group) SAE Aripiprazole: 11 (6.6%) Placebo: 8 (4.8%) NS

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
	Woo, 2011 ³⁰ High 22134973	<u>Time to Relapse</u> 6 months NS	YMRS 6 months NS MADRS 6 months NS	CGI-CP-S 6 months NS	<u>Weight gain >7%</u> NS <u>Overall Withdrawal</u> Aripiprazole 17/40 (38.7%) Placebo 18/43 (41.9%) NS Withdrawal lack of <u>efficacy</u> Aripiprazole 6/40 (15%) Placebo 8/43 (18.6%) NS <u>Withdrawal for AE</u> Aripiprazole 0% Placebo 9.3% p=0.049	SAE Aripiprazole: 5% Placebo: 11% Included 1 suicide EPS No discontinuation in either group
	Carlson, 2012 ²⁹ High 22329471	Time to Relapse 52 weeks Hazard Ratio 0.67 (0.45, 1.00) NS	NA (Attrition 66%)	NA (Attrition 66%)	<u>Withdraw for AE</u> Aripiprazole 14/176 (8%) Placebo 12/165 (7.3%)	SAE Aripiprazole 5/176 (2.8%) Placebo 9/165 (5.5%) No deaths or suicides At least 1 EPS AE Aripiprazole 28/176 (15.9%) Placebo 15/165 (9.1%) Weight gain >7% Aripiprazole 11% Placebo 3.5% p=0.007

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
Divalproex + lithium vs. placebo + lithium alone	Kemp, 2009 ³¹ High 19192457	Time to Relapse 52 weeks Hazard Ratio 0.72 (0.32, 1.65) NS	NA (Attrition 74%)	NA (Attrition 74%)	<u>NA</u>	No SAEs mentioned. <u>EPS</u> Tremors NS
Olanzapine + mood stabilizer vs. placebo + mood stabilizer	Tohen, 2004 ³² Industry 15056579 extension of Tohen, 2002 ³³ 11779284	Time to relapse 18 months Log rank NS	NA (Attrition 78%)	NA	<u>Time to overall withdrawal</u> 18 month Favors Olanzapine Log rank p=0.049	SAE not reported EPS No difference between groups
Oxcarbazepine + lithium vs. placebo + lithium	Vieta, 2008 ³⁹ Moderate 18346292	<u>Time to relapse</u> ¹ 52 week NS Kaplan Meier log-rank <u>Relapse Rate</u> 52 week NS	<u>YMRS Change</u> 52 week NS <u>MADRS Change</u> 52 week NS	<u>CGI-BP-M</u> 52 week NS p=0.45	<u>Weight Gain</u> ≥7% of baseline Oxcarbazepine 19.2% Placebo 6.9% <u>Withdrawal for AE</u> Oxcarbazepine 3 Placebo 2 <u>Withdrawal for lack of efficacy</u> Oxcarbazepine 0 Placebo 2	<u>Serious Adverse Events</u> 52 week 3 events – Oxcarbazepine 3 events – Placebo
Gabapentin + mood stabilizers vs. placebo + mood stabilizers	Vieta, 2006 ⁴⁰ High 16649836	<u>Time to Relapse</u> 52 week NS HR 1.344	YMRS Change 52 week NS HAM-D 52 week NS	<u>CGI-BP-M Change</u> 52 week Favors Gabapentin 1.5% (95% CI 0.5,2.5) p=0.0046	<u>Withdrawal AE</u> Gabapentin 1 (8%) Placebo 1 (8%) <u>Withdrawal lack of efficacy</u> Gabapentin 2 (15%) Placebo 1 (8%)	Gabapentin: 1 Myocardial Infarction Placebo: No Events Reported

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
Perphenazine + mood stabilizers vs. placebo + mood stabilizers	Zarate, 2004 ⁴¹ High 14702269	<u>Time to Relapse to Depression</u> Favors placebo Perphenazine: 157 days (SE 10) Placebo: None Occurred p<0.03 <u>Depressive Relapse</u> Favors placebo Perphenazine 21% Placebo 0% <u>Manic Relapse</u> NS Perphenazine 5% Placebo 11%	NR	NR	<u>Overall Withdrawal</u> Perphenazine 10 (52.6%) Placebo 3 (16.7%)	NR
Quetiapine + mood stabilizers vs. placebo + mood stabilizers	Suppes, 2009 ³⁴ High 19289454	Time to Recurrence of mood event 104 weeks Hazard Ratio 0.32 (0.24, 0.42) risk reduction 68% Favors Quetiapine (not dependent on rapid cycling)	70% risk reduction in time to recurrence of mania 67% risk reduction in time to recurrence of depression	Not applicable	<u>Overall Withdrawal</u> Quetiapine 200/310 Placebo 247/313 Loss to followup and Other categories greater than adverse event or lack of efficacy categories	SAE Quetiapine: 18 (5.8%) Placebo: 7 (2.2%)
	Vieta, 2008 ³⁵ High 18579216	Time to Recurrence of mood event 104 weeks Hazard Ratio 0.28 (0.21, 0.37) risk reduction 72% Favors Quetiapine	Time to Recurrence of mania 104 weeks Hazard Ratio 0.30 (0.20, 0.44) Favors Quetiapine Time to Recurrence of depression 104 weeks Hazard Ratio 0.26 (0.17, 0.41) Favors Quetiapine	Not applicable	<u>Overall Withdrawal</u> Quetiapine 123/336 Placebo 233/367 Loss to followup and Other categories greater than adverse event or lack of efficacy categories	SAE Quetiapine: 5 (1.5%) Placebo: 20 (5.4%)

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
Risperidone long acting injectable + treatment as usual vs. placebo + treatment as usual	Macfadden, 2009 ³⁷ High 19922552	Relapse - Time to (DSM diagnosis for acute mood episode + other complicated criteria) 52 weeks Log rank test p=0.01 Favors Risperidone	YMRS 52 weeks Favors Risperidone (only figure) MADRS 52 weeks NS	CGI-BP-S 52 weeks Favors Risperidone (only figure)	<u>Overall Withdrawal</u> Risperidone 26/65 (40%) Placebo 34/59 (57.6%) NS Withdrawal lack of <u>efficacy</u> Risperidone 13/65 (20%) Placebo 23/59 (39%) p=0.02 <u>Withdrawal for AE</u> Risperidone 3/65 (4.6%) Placebo 1/59 (1.7%) NS	At least 1 SAE Risperidone: 9 Placebo: 13 Deaths Risperidone: 1 Placebo: 2 (1 of suicide 3 months after study) Suicide ideation: Risperidone: 1 Placebo: 3 EPS NS
Risperidone long-acting injectable + treatment as usual vs. treatment as usual	Bobo, 2011 ³⁶ High 22104634	<u>Any cause relapse</u> 52 weeks NS	YMRS 52 weeks NS MADRS 52 weeks NS	CGI-S 52 weeks NS	<u>Overall Withdrawal</u> Risperidone 4/25 Placebo 6/25 NS Withdrawal lack of <u>efficacy</u> Risperidone 6/40 (15%) Placebo 8/43 (18.6%) NS <u>Withdrawal for AE</u> Risperidone 0% Placebo 9.3% p=0.049	No suicide attempts; NS for suicide ideation EPS NS

Drug	Study RoB PMID	Responder/Remitter	Symptom	Function	Other	AE
Ziprasidone + mood stabilizers vs. placebo + mood stabilizers	Bowden, 2010 ³⁸ High 20122373 (also 22999893)	<u>Time to relapse</u> 26 weeks Log rank test p=0.01 Favors Ziprasidone	YMRS 26 weeks Least squares mean difference -3.27 (0.83) p<0.001 Favors Ziprasidone MADRS NS	NR	<u>Weight gain >7%</u> NS <u>Overall Withdrawal</u> Ziprasidone 43/127 Placebo 58/113 p=0.007 <u>Withdrawal lack of efficacy</u> Ziprasidone 9/127 Placebo 22/113 p=0.004 <u>Withdrawal for AE</u> Ziprasidone 11/127 Placebo 15/113 NS	SAE Ziprasidone: 11/127 8.7% Placebo: 6/112 5.4% No deaths

Abbreviations: AE=Adverse Events; CGI-BP-M=Clinical Global Impressions Scale-Bipolar-modified (for long-term follow-up); CGI-BP-S=Clinical Global Impressions, Bipolar, Severity Scale; CGI-S=Clinical Global Impressions, Severity Scale; CI=Confidence Interval; DSM=Diagnostic and Statistical Manual of Mental Disorders; EPS=extrapyramidal symptoms; HAM-D=Hamilton Scale for Depression; HR=Hazard Ratio; MADRS=Montgomery-Asberg Depression Rating Scale; MID=Minimally important difference; NA=Not applicable; NS= Not Significant; PMID=PubMed Identification Number; RoB=Risk of Bias; SAE=Serious Adverse Events; SE=standard error; YMRS = Young Mania Rating Scale;

Appendix Table I14. Strength of evidence assessment: combination therapy versus placebo for maintenance

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Aripiprazole + mood stabilizer vs. placebo + mood stabilizer	Time to Relapse 52 wks YMRS 6 mths MADRS 6 mths CGI 6 mths Withdrawals	2 RCT (n=420)	See table above	High	Unknown (over 2 time periods; Inconsistent if combined)	Direct	Imprecise	Insufficient
Divalproex + lithium vs. placebo + lithium alone	Time to relapse 26 weeks	1 RCT (n=31)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Olanzapine + mood stabilizer vs. placebo + mood stabilizer	Time to relapse 18 months	1 RCT (n=99)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Oxcarbazepine + lithium vs. placebo + lithium	Time to relapse 52 wks YMRS 52 wks HAM-D 52 wks CGI-BP-M 52 wks	1 RCT (n=55)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Gabapentin + mood stabilizers vs. placebo + mood stabilizers	Time to relapse 52 wks YMRS 52 wks HAM-D 52 wks CGI-CP-M 52 wks	1 RCT (n=25)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Perphenazine + mood stabilizers vs. placebo + mood stabilizers	Time to depression relapse 6 mths	1 RCT (n=37)	See table above	High	Unknown	Direct	Imprecise	Insufficient
Quetiapine + mood stabilizers vs. placebo + mood stabilizers	Time to recurrence any mood, 102 wks time to mania 102 wks time to depression 102 wks	2 RCT (n=1329)	See table above	High	Consistent	Direct	Imprecise	Insufficient
Risperidone long acting injectable + treatment as usual vs. placebo + treatment as usual	Time to recurrence 52 wks YMRS 52 wks MADRS 52 wks CGI 52 wks Withdrawals	2 RCT (n=174)	See table above	High	Inconsistent	Direct	Imprecise	Insufficient

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Ziprasidone + mood stabilizers vs. placebo + mood stabilizers	Relapse Risk 26 wks YMRS 26 wks MADRS 26 wks Withdrawals	1 RCT Combination (n=240)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI=Clinical Global Impressions; CGI-BP-M=Clinical Global Impressions Scale-Bipolar-modified (for long-term follow-up); HAM-D=Hamilton Scale for Depression; MADRS=Montgomery-Asberg Depression Rating Scale; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.

2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research

Appendix Table I15. Outcomes summary: combination therapy versus active control for maintenance

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Lithium + valproate vs. valproate vs. lithium	Balance Investigators, 2010 ¹⁸ 20092882	<u>Time to new intervention for emerging mood episode</u> 24 months Hazard ratio Favors L+V over Valproate NS for L+V vs. Lithium	NR	GAF NS	EuroQol (EQ-5D) (quality of life) NS Overall Withdrawal L+V: 21/110 Lithium: 23/110 Valproate: 23/110 Withdrawal lack of efficacy NR Withdrawal adverse events L+V: 11/110 Lithium: 6/110 Valproate: 4/110	<u>SAE</u> NS Valproate: 7 SAE including 3 deaths Lithium: 5 SAE including 2 deaths L+V: 4 SAE including 1 death (only one deemed due to study – did not report which)

Drug	Study Comparison PMID	Responder/Remitter	Symptom	Function	Other	AE
Quetiapine + personalize treatment vs. Lithium + personalized treatment	Nierenberg, 2016 ⁴² 26845264	NR	YMRS 24 week NS (model-based effect) MADRS 24 week NS (model-based effect)	CGI-EI 24 weeks NS (model-based effect)	<u>Overall Withdrawal</u> Quetiapine: 60/180 24.8% Lithium: 58/182 24.2% <u>Withdrawal lack of efficacy</u> NR <u>Withdrawal serious adverse events</u> Quetiapine: 2/180 Lithium: 0/182 24	<u>Death</u> Quetiapine: 0 Lithium: 2
Valproic acid + Aripiprazole vs. Lithium + Aripiprazole	Vieta, 2010 ⁴³ 20429835	Remission (YMRS<12, MADRS<8) At least 2/3 patients in both groups after 40 weeks	YMRS 46 weeks Mean change + Lithium: -2.7 (-4.5, -0.7) + Valproic: -5.8 (-7.2, -4.3) MADRS 46 weeks Mean change + Lithium: -0.8 (-2.6, 1.0) + Valproic: -1.2 (-2.6, 0.3)	NR	<u>Overall Withdrawal</u> +Lithium: 53/108 49.1% +Valproic: 84/175 48% <u>Withdrawal lack of efficacy</u> +Lithium: 1/108 0.9% +Valproic: 10/175 5.7% <u>Withdrawal adverse events</u> +Lithium: 20/108 18.5% +Valproic: 24/175 13.7%	<u>SAE</u> +Lithium: 15 (14.2%) 1 patient suicidal ideation 1 lithium overdose death (50 days after last study dose) +Valproic: 15 (8.6%) EPS +Lithium: 24 (22.6%) +Valproic: 38 (21.8%)

Abbreviations: CGI-EI=Clinical Global Impressions-Efficacy Index; EPS=extrapyramidal symptoms; GAF=General Assessment of Functioning Scale; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAE=Severe Adverse Events; YMRS = Young Mania Rating Scale

Appendix Table I16. Strength of evidence assessment: combination therapy versus active control for maintenance

Comparison	Outcome	# Studies/ Design (n analyzed)	Finding or Summary Statistic Outcome Timing	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Lithium + valproate vs. valproate vs. lithium	Time to Relapse 24 mths GAF 24 mths EuroQual 24 mths Withdrawals	1 RCT (n=330)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Quetiapine + personalize treatment vs. Lithium + personalized treatment	YMRS 24 wks MADRS 24 wks CGI 24 wks Withdrawals	1 RCT (n=482)	See table above	Moderate	Unknown	Direct	Imprecise	Insufficient
Valproic acid + Aripiprazole vs. Lithium + Aripiprazole	Remission 46 wks YMRS 46 wks MADRS 46 wks Withdrawals	1 RCT open label extension (n=28)	See table above	High	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CGI= Clinical Global Impressions; GAF=General Assessment of Functioning Scale; MADRS=Montgomery-Asberg Depression Rating Scale; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Notes:

1. Publication bias for antipsychotics, antidepressants, and behavioral interventions for depressive disorders is suspected.
2. Data were generally imprecise due to missing data from high attrition rates, which was commonly dealt with by Last Observation Carried Forward (LOCF). LOCF requires an assumption that the health status of patients who dropped out of the trial would not have changed had future observations been recorded, a strong assumption in the context of bipolar disorder research.

References for Appendix I

1. Bowden CL, Calabrese JR, McElroy SL, et al. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Divalproex Maintenance Study Group. *Archives of General Psychiatry*. 2000 May;57(5):481-9. PMID: 10807488.
2. Gyulai L, Bowden CL, McElroy SL, et al. Maintenance efficacy of divalproex in the prevention of bipolar depression. *Neuropsychopharmacology*. 2003 Jul;28(7):1374-82. PMID: 12784116.
3. Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. *American Journal of Psychiatry*. 2010 Jul;167(7):792-800. doi: <http://dx.doi.org/10.1176/appi.ajp.2009.09020284>. PMID: 20360317.
4. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder.[Erratum appears in Arch Gen Psychiatry. 2004 Jul;61(7):680]. *Archives of General Psychiatry*. 2003 Apr;60(4):392-400. PMID: 12695317.
5. Calabrese JR, Bowden CL, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *Journal of Clinical Psychiatry*. 2003 Sep;64(9):1013-24. PMID: 14628976.
6. Prien RF, Point P, Caffey EM, et al. Prophylactic efficacy of lithium carbonate in manic-depressive illness: Report of the veterans administration and national institute of mental health collaborative study group. *Archives of General Psychiatry*. 1973;28(3):337-41. doi: 10.1001/archpsyc.1973.01750330035006. PMID: 4569674.
7. Weisler RH, Nolen WA, Neijber A, et al. Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study). *Journal of Clinical Psychiatry*. 2011 Nov;72(11):1452-64. doi: <http://dx.doi.org/10.4088/JCP.11m06878>. PMID: 22054050.
8. Calabrese JR, Sanchez R, Jin N, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: A double-blind, placebo-controlled, 52-week randomized withdrawal study. *Journal of Clinical Psychiatry*. 2017 March;78(3):324-31. doi: <http://dx.doi.org/10.4088/JCP.16m11201>. PMID: 28146613 PMID/615221995 Embase.
9. Keck PE, Jr., Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. *Journal of Clinical Psychiatry*. 2006 Apr;67(4):626-37. PMID: 16669728.
10. Hartong EG, Moleman P, Hoogduin CA, et al. Prophylactic efficacy of lithium versus carbamazepine in treatment-naïve bipolar patients. *Journal of Clinical Psychiatry*. 2003 Feb;64(2):144-51. PMID: 12633122.
11. Greil W, Ludwig-Mayerhofer W, Erazo N, et al. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders--a randomised study. *Journal of Affective Disorders*. 1997 Apr;43(2):151-61. PMID: 9165384.
12. Greil W, Kleindienst N, Erazo N, et al. Differential response to lithium and carbamazepine in the prophylaxis of bipolar disorder. *Journal of Clinical Psychopharmacology*. 1998 Dec;18(6):455-60. PMID: 9864077.
13. Greil W, Kleindienst N. The comparative prophylactic efficacy of lithium and carbamazepine in patients with bipolar I disorder. *International Clinical Psychopharmacology*. 1999 Sep;14(5):277-81. PMID: 10529070.
14. Greil W, Kleindienst N. Lithium versus carbamazepine in the maintenance treatment of bipolar II disorder and bipolar disorder not otherwise specified. *International Clinical Psychopharmacology*. 1999 Sep;14(5):283-5. PMID: 10529071.
15. Kleindienst N, Greil W. Differential efficacy of lithium and carbamazepine in the prophylaxis of bipolar disorder: results of the MAP study. *Neuropsychobiology*. 2000;42 Suppl 1:2-10. PMID: 11093063.
16. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium versus divalproex in rapid-cycling bipolar disorder. *American Journal of Psychiatry*. 2005 Nov;162(11):2152-61. PMID: 16263857.

17. Calabrese JR, Suppes T, Bowden CL, et al. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid-cycling bipolar disorder. Lamictal 614 Study Group. *Journal of Clinical Psychiatry*. 2000 Nov;61(11):841-50. PMID: 11105737.
18. Balance investigators, Geddes JR, Goodwin GM, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet*. 2010 Jan 30;375(9712):385-95. doi: [http://dx.doi.org/10.1016/S0140-6736\(09\)61828-6](http://dx.doi.org/10.1016/S0140-6736(09)61828-6). PMID: 20092882.
19. Tohen M, Calabrese JR, Sachs GS, et al. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. *American Journal of Psychiatry*. 2006 Feb;163(2):247-56. PMID: 16449478.
20. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. *American Journal of Psychiatry*. 2003 Jul;160(7):1263-71. PMID: 12832240.
21. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania.[Erratum appears in *Am J Psychiatry*. 2005 Feb;7(1):102]. *American Journal of Psychiatry*. 2002 Jun;159(6):1011-7. PMID: 12042191.
22. Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biological Psychiatry*. 2010 Jul 15;68(2):156-62. doi: <http://dx.doi.org/10.1016/j.biopsych.2010.01.015>. PMID: 20227682.
23. Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *European Neuropsychopharmacology*. 2012 Nov;22(11):825-35. doi: <http://dx.doi.org/10.1016/j.euroneuro.2012.03.004>. PMID: 22503488.
24. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. *American Journal of Psychiatry*. 2005 Jul;162(7):1281-90. PMID: 15994710.
25. Berwaerts J, Melkote R, Nuamah I, et al. A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. *Journal of Affective Disorders*. 2012 May;138(3):247-58. doi: <http://dx.doi.org/10.1016/j.jad.2012.01.047>. PMID: 22377512.
26. Amsterdam JD, Lorenzo-Luaces L, Soeller I, et al. Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study. *Journal of Affective Disorders*. 2015 06 Jul;185:31-7. doi: <http://dx.doi.org/10.1016/j.jad.2015.05.070>. PMID: 26143402 (pubmed) 2015175772 (embase).
27. Newport DJ, Stowe ZN, Viguera AC, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disorders*. 2008 May;10(3):432-6. doi: <http://dx.doi.org/10.1111/j.1399-5618.2007.00565.x>. PMID: 18402631.
28. Marcus R, Khan A, Rollin L, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disorders*. 2011 Mar;13(2):133-44. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00898.x>. PMID: 21443567.
29. Carlson BX, Ketter TA, Sun W, et al. Aripiprazole in combination with lamotrigine for the long-term treatment of patients with bipolar I disorder (manic or mixed): a randomized, multicenter, double-blind study (CN138-392). *Bipolar Disorders*. 2012 Feb;14(1):41-53. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00974.x>. PMID: 22329471.

30. Woo YS, Bahk WM, Chung MY, et al. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. *Human Psychopharmacology*. 2011 Dec;26(8):543-53. doi: <http://dx.doi.org/10.1002/hup.1240>. PMID: 22134973.
31. Kemp DE, Gao K, Ganocy SJ, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. *Journal of Clinical Psychiatry*. 2009 Jan;70(1):113-21. PMID: 19192457.
32. Tohen M, Chengappa KN, Suppes T, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *British Journal of Psychiatry*. 2004 Apr;184:337-45. PMID: 15056579.
33. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Archives of General Psychiatry*. 2002 Jan;59(1):62-9. PMID: 11779284.
34. Suppes T, Vieta E, Liu S, et al. Maintenance treatment for patients with bipolar I disorder: results from a north american study of quetiapine in combination with lithium or divalproex (trial 127). *American Journal of Psychiatry*. 2009 Apr;166(4):476-88. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.08020189>. PMID: 19289454.
35. Vieta E, Suppes T, Eggens I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). *Journal of Affective Disorders*. 2008 Aug;109(3):251-63. doi: <http://dx.doi.org/10.1016/j.jad.2008.06.001>. PMID: 18579216.
36. Bobo WV, Epstein RA, Lynch A, et al. A randomized open comparison of long-acting injectable risperidone and treatment as usual for prevention of relapse, rehospitalization, and urgent care referral in community-treated patients with rapid cycling bipolar disorder. *Clinical Neuropharmacology*. 2011 Nov-Dec;34(6):224-33. doi: <http://dx.doi.org/10.1097/WNF.0b013e318237709a>. PMID: 22104634.
37. Macfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009 Dec;11(8):827-39. doi: <http://dx.doi.org/10.1111/j.1399-5618.2009.00761.x>. PMID: 19922552.
38. Bowden CL, Vieta E, Ice KS, et al. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *Journal of Clinical Psychiatry*. 2010 Feb;71(2):130-7. doi: <http://dx.doi.org/10.4088/JCP.09m05482yel>. PMID: 20122373.
39. Vieta E, Cruz N, Garcia-Campayo J, et al. A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. *International Journal of Neuropsychopharmacology*. 2008 Jun;11(4):445-52. doi: <http://dx.doi.org/10.1017/S1461145708008596>. PMID: 18346292.
40. Vieta E, Manuel Goikolea J, Martinez-Aran A, et al. A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. *Journal of Clinical Psychiatry*. 2006 Mar;67(3):473-7. PMID: 16649836.
41. Zarate CA, Jr., Tohen M. Double-blind comparison of the continued use of antipsychotic treatment versus its discontinuation in remitted manic patients. *American Journal of Psychiatry*. 2004 Jan;161(1):169-71. PMID: 14702269.
42. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *Journal of Clinical Psychiatry*. 2016 Jan;77(1):90-9. doi: <http://dx.doi.org/10.4088/JCP.14m09349>. PMID: 26845264.
43. Vieta E, Owen R, Baudelet C, et al. Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. *Current Medical Research & Opinion*. 2010 Jun;26(6):1485-96. doi: <http://dx.doi.org/10.1185/03007991003779380>. PMID: 20429835.

Appendix J. Psychoeducation

Appendix Table J1. Characteristics of eligible studies: psychoeducation vs. inactive comparators by year then first author

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Barnes, 2015 ¹ RCT Australia Non-Government Moderate 25554993	N = 233 Age 40 (18-58) Female 72% White NR BP I 88% BP II 12% Outpatient	No current clinical state excluded; Individuals with BP I or II (DSM-IV) with euthymia or a current manic or depressive episode and taking medication for BP. Labs/Other Conditions	Internet-based psychoeducation (Road to Recovery for Bipolar Disorder) focused on managing symptoms, medication, psychological approaches, relationships, and lifestyle. Participants had access to 10 sessions of cognitive behavioral therapy as homework -20 online sessions, first 8 sessions weekly, 9 and 10 every 2-week period, and 11-20 were monthly	Internet-based attention control (Virtual Highway for Bipolar Disorder) -20 online sessions, first 8 sessions weekly, 9 and 10 every 2- week period, and 11-20 were monthly	12 months	Time to Relapse Hospitalization Relapse (Return of significant symptoms after a remission of at least 8 weeks, DSM-IV) Withdrawal 28%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Gumus, 2015 ² RCT Turkey NR High 26001717	N = 82 Age 39 (27-52) Female 48% Race NR BP I 89% BP II 11% Outpatient	Euthymic; Individuals with BP I or II (DSM-VI) who received standard medical treatment and were euthymic (YMRS>6, HDRS <17) for at least 3 months. Other Mental Health	Psychoeducation focused on illness education, warning signs, medication and side effects, and problem solving skills as well as standard clinical monitoring - 60 minute sessions, once per week, for 4 weeks	Standard clinical follow up (not described) -Duration of study	12 months	Hospitalization Relapse (Emergency of new clinical episode, YMRS≥20, HDRS≥17 or YMRS≥20 and HDRS≥12) Withdrawal 5%
de Barros Pellegrinelli, 2013 ³ RCT Brazil Non-Government High 22943487	N = 55 Age 44 (22-66) Female 69% White NR BP NR Outpatient	Euthymic/Maintenance; Individuals diagnosed with BP I or II (DSM-IV), in remission for at least 1 month (HDRS <7 and YMRS <6) Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders	Psychoeducation consisting of 15 min introduction, 30 min education, 30 min discussion and psychological support, and 15 min for conclusion -16 twice-weekly 90- minute sessions	Sessions promoting relaxation consisting of informal conversation and relaxation using three different types of exercises -16 twice-weekly 90-minute sessions	12 months	HDRS YMRS GAF Withdrawal 45%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Javadpour, 2013 ⁴ RCT Iran Non-Government High 23642977	N = 108 Age NR (18-60) Female 51% White NR BP NR Outpatient	Euthymic/Maintenance; Individuals with BP with a history of at least 2 episodes of relapse in past 2 years or at least 3 episodes in past 5 years, and euthymic (HAM-D <8 and BRMS <9) First Manic Episode	Psychoeducation focusing on understanding bipolar, familiarization with symptoms understanding signs of an episodes, awareness of causes and prognosis, education about the function, types and adverse side effect of mood stabilizer medication, functions, types and adverse effects of anti-manic and antidepressant medications, and risks of discontinuing medications - Eight 50-minute weekly session	Standard pharmacotherapy (discretion of treating psychiatrist of their choice)	18 months	Relapse (HAM-D >17 or BRMS >15) Hospitalizations BRMS HDRS Withdrawal 20%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Smith, 2011 ⁵ RCT United Kingdom Government Low 22017225	N = 50 Age 44 (22-66) Female 62% White 98% BP I 86% BP II 12% BP NOS 2% Outpatient	Euthymic/Maintenance; DSM-IV diagnosis of bipolar disorder currently in clinical remission, and not fulfilling diagnostic criteria for a depressive, manic or mixed affective episode during the preceding 3 months Neurological Disorders	Internet-based psychoeducation focusing on causes, role of medication, lifestyle changes, relapse prevention and early intervention, psychological approaches, gender-specific considerations, and advice for family and careers - Initial face-to-face meeting with psychiatrist to learn how to use program followed by four months of every- other-week online psychoeducation	Treatment as usual: Usual care delivered in a collaborative model between general practitioners and community mental health teams.	6 months	Relapse MADRS YMRS GAF FAST WHO-QOL-bref Withdrawal 26%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Sajatovic, 2009 ⁶ RCT United States Government Low 19723732	N = 164 Age 41 (18-76) Female 68% White 60% BP NR Outpatient	No current clinical state excluded; Individuals with type I or type II bipolar disorder (MINI) Other Conditions	Group psychoeducation (Life Goals Program) focusing on illness education, medication adherence, management, goal setting, and problem solving -6 weekly sessions followed by optional monthly group sessions	Treatment as usual: Treatment at community mental health care including medication management and psychosocial therapy and counseling	12 months	HAM-D GAS YMRS Withdrawal 22%
Colom, 2009 ⁷ Colom, 2003 ⁸ Spain Non-Government Low 12695318 19252157	N = 120 Age NR (18-65) Female 63% White NR BP I 83% BP II 17% Outpatient	Euthymic/Maintenance; Diagnosis of BP I or II, euthymic (YMRS <6, HDRS <8) for at least 6 months, having sufficient data on the prior course of illness collected from a prospective follow-up of at least 24 months Other Mental Health; Neurological Disorders	Group psychoeducation (and pharmacologic treatment) that focused on illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and life-style regularity -21 weekly 90- minute sessions	Standard pharmacologic treatment and group meetings with psychologists without any psychosocial feedback (unless necessary for patient interaction) -20 weekly group sessions	5 years	Relapse (DSM-IV criteria for new acute episode and one of following: YMRS≥ 20 or YMRS≥12 or HDRS≥17, or YMRS≥ and HDRS≥20) Hospitalizations Withdrawal 18%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Colom, 2003b ⁹ RCT Spain Non-Government Low 14628987	N = 50 Age 35 (18-57) Female 72% White NR BP I 100% Outpatient	Euthymic/Maintenance; A lifetime diagnosis of BP I (DSM-IV), euthymic (YMRS <6, HAM-D <8) for at least 6 months, data on the prior course of illness collected from a prospective follow- up of at least 24 months, good treatment compliance during at least 6 months prior to enrollment. Other Mental Health; Neurological Disorders; Taking Other Meds	Group psychoeducation (and standard treatment) focused on illness awareness, treatment compliance, prodromal symptoms and relapse, lifestyle regularity, symptom monitoring, treatment adherence, and illness management skills. -20 weekly group sessions for 90 minutes	Standard pharmacologic treatment and group meetings with psychologists without any psychosocial feedback (unless necessary for patient interaction). Therapists encouraged communication between patients. -20 weekly group sessions	2 years	Relapse (DSM-IV criteria and HAM-D or YMRS ≥12) Hospitalizations Withdrawal 0%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Weiss, 2000 ¹⁰ CCT United States Government High 10847311	N = 45 Age 36 (18-54) Female 49% White 87% BP I 73% BP II 18% BP NOS 9% Outpatient	No current clinical state excluded; Current diagnoses of BP and substance dependence, substance use within 30 days, and taking a mood stabilizer Neurological Disorders; Other Conditions (which would preclude attendance)	Psychoeducation focused on acceptance, self- help, identifying and fighting triggers, medication adherence, coping skills, and similarities between recovery and relapse for bipolar and substance abuse -12-20 weekly group therapy, 60 minutes per session	Treatment as usual/No treatment (not described) with 6 monthly assessments	6 months	YMRS HAM-D Hospitalizations Withdrawal 47%
Perry, 1999 ¹¹ RCT United Kingdom Government Moderate 9888904	N = 69 Age 45 (23-67) Female 68% White 91% BP I 91% BP II 9% Outpatient	Maintenance; A lifetime diagnosis of bipolar disorder elicited by a trained research assistant using a standardized psychiatric interview and two or more relapses, one in the previous 12 months. Substance Abuse; Neurological Disorders	Psychoeducation (and routine treatment) involving 12 individual treatment sessions that focused on identifying prodromal symptoms and producing and rehearsing an action plan once prodromes had been recognized	Treatment as usual: Drug treatment, monitoring of mood and adherence to treatment, education about BP, and inpatient care if necessary.	18 months	Relapse (Minimum of five days of symptoms of mania, hypomania, mixed affective disorder, or major depression according to the standardized symptom criteria) SPS Withdrawal 14%

Abbreviations: BP=bipolar disorder; BRMS= Bech–Rafaelsen Mania Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HDRS= Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MINI=MINI International Neuropsychiatric Interview; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; SPS=Social Phobia Scale; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table J2. Summary risk of bias assessments: psychoeducation vs. inactive comparators by year then first author

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Barnes, 2015 ¹ Non-Government 25554993	Moderate	Suspected bias due to incomplete reporting of outcomes (unable to separate outcomes by study arm).
de Barros Pellegrinelli, 2013 ³ Non-Government 22943487	High	Suspected bias due to high attrition rate (45%).
Gumus, 2015 ² NR 26001717	High	Suspected bias due to procedures for randomization and unclear reporting of study attrition.
Javadpour, 2013 ⁴ Non-Government 23642977	High	Suspected bias due to unclear reporting of outcomes (format of reporting makes it difficult to interpret results).
Smith, 2011 ⁵ Government 22017225	Low	No significant suspected biases.
Sajatovic, 2009 ⁶ Government 19723732	Low	No significant suspected biases.
Colom, 2009 ⁷ Colom, 2003 ⁸ Non-Government 12695318 19252157	Low	No significant suspected biases.
Colom, 2003b ⁹ Non-Government 14628987	Low	No significant suspected biases.
Weiss, 2000 ¹⁰ Government 10847311	High	Suspected selection bias (subjects are not randomized) and unclear reporting of attrition and outcome data.
Perry, 1999 ¹¹ Government 9888904	Moderate	Suspected bias due to lack of blinding. Assessors appeared to have access to full set of information/notes on subjects.

Abbreviations: PMID=PubMed Identification Number

Appendix Table J3. Outcomes summary: psychoeducation vs. inactive comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Barnes 2015 ¹ 25554993	<u>Relapse</u> 12 months, Any Type NS at any threshold for recurrence (low, moderate, high). Low: HR=0.86; p=0.48 Moderate: HR= 0.82; p=0.33 High: HR=0.91; p=0.65 <u>Time to Relapse</u> 12 months, Any Type NS at any threshold for recurrence (low, moderate, high).	NR	NR	<u>Hospitalizations</u> 12 months NS; p=0.90	NR
Gumus, 2015 ² 26001717	<u>Relapse*</u> 12 months, Any Type NS OR=0.50 (95% CI 0.14, 1.57); p=0.21	NR	NR	<u>Hospitalizations</u> 12 months NS, Number of Hospitalizations Psychoeducation: 0 (0%) Comparator: 3 (7.3%)	NR
de Barros Pellegrinelli 2013 ³ 22943487	NR	<u>Depression</u> 12 months, HDRS No difference between groups ES=0.007; p=0.82 <u>Mania</u> 12 months, YMRS NS ES=0.016; p=0.72	<u>Global Function</u> 12 months, GAF NS ES=0.03; p=0.59	NR	NR
Javadpour 2013 ⁴ 23642977	<u>Relapse</u> 18 months, Any Type Favors psychoeducation; p=0.00	<u>Depression</u> 18 months, HDRS Favors psychoeducation ; p=0.00 <u>Mania</u> 18 months, BRMS Favors psychoeducation; p=0.00	NR	<u>Hospitalizations</u> 18 months, Any Type Favors psychoeducation; p=0.00 Average Number of Hospitalizations Psychoeducation: 0.22 Comparator: 1.41	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Smith 2011 ⁵ 22017225	<u>Relapse*</u> 10 months, Depressive NS OR=1.75 (95% CI 0.39, 7.87); p=0.31 10 months, Manic NS OR=0.92 (95% CI 0.15, 5.36); p=0.61	<u>Depression*</u> 10 months, MADRS NS ES=-0.17 (95% -0.82, 0.48) <u>Mania*</u> 10 months, YMRS NS ES=-0.25 (95% -0.90, 0.40)	<u>Global Function*</u> 10 months, GAF NS ES=0.26 (95% CI -0.39, 0.91) <u>Global Function*</u> 10 months, FAST NS ES=0.26 (95% CI, -0.39, 0.91) <u>Quality of Life*</u> 10 months, WHO-QOL-bref NS ES=-0.04 (95% CI -0.69, 0.60)	NR	NR
Sajatovic 2009 ⁶ 19723732	NR	<u>Depression*</u> 6 months, HAM-D NS ES=0.03 (95% CI -0.35, 0.42) <u>Mania*</u> 6 months, YMRS NS ES=-0.16 (95% CI -0.54, 0.23)	<u>Global Function*</u> 6 months, GAF NS ES=-0.03 (95% CI -0.43, 0.36)	NR	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Colom 2003 ⁸ 12695318 Colom 2009 ⁷ 19252157	<u>Relapse*</u> 2 years, Any Type Favors psychoeducation OR=0.18 (95% CI 0.05, 0.56); p=0.00	NR	NR	<u>Hospitalizations</u> 2 Years NS; p=0.24 Number of Hospitalizations Psychoeducation: 14 (25%) Comparator: 21 (35%) 5 Years NS; p=0.28 Number of Hospitalizations Psychoeducation: 17 (30.4%) Comparator: 24 (40%)	NR
Colom 2003b ⁹ 14628987	<u>Relapse*</u> 2 years, Any Type Favors psychoeducation OR=0.13 (95% CI 0.01, 0.77); p=0.02	NR	NR	<u>Hospitalizations</u> 2 Years Favors psychoeducation; p=0.01 Number of Hospitalizations Psychoeducation: 2 (8.0%) Comparator: 9 (36%)	NR
Weiss 2000 ¹⁰ 10847311	NR	<u>Depression</u> 6 months, HAM-D NS <u>Mania</u> 6 months, YMRS Favors psychoeducation; p<0.04	NR	<u>Hospitalizations</u> 6 months NS Number of Hospitalizations Psychoeducation: 8 (38.1%) Comparator: 10 (41.7%)	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Perry 1999 ¹¹ 9888904	<u>Relapse*</u> 6 months, Depressive NS OR=1.44 (95% CI 0.45, 4.73); p=0.60 18 months, Depressive NS OR=2.03 (95% CI 0.69, 6.00); p=0.22 6 months, Manic Favors psychoeducation OR=0.14 (95% CI 0.01, 0.75); p=0.01 18 months, Manic Favors psychoeducation OR=0.28 (95% CI 0.09, 0.87); p=0.02	NR	<u>Social Function</u> 6 months, SPS NS Mean Difference=0.44 (95% CI -0.78, 1.65) 18 months, SPS Favors psychoeducation Mean Difference =1.97 (95% CI 0.71, 3.23)	NR	NR

Abbreviations: AE=Adverse Events; BRMS=Bech-Rafaelsen Mania Scale; CI=Confidence Interval; ES=Effect Size; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HDRS=Hamilton Depression Rating Scale; HR=Hazard Ratio; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OR= Odds Ratio; PMID=PubMed Identification Number; SPS=Social Phobia Scale; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table J4. Summary of strength of evidence: psychoeducation vs. inactive comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	6 months 7-12 months 12+ months	7 RCTs (n=712)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Depression	6 months 7-12 months 12+ months	5 RCTs (n=422)	No difference between groups across a range of outcome timepoints.	High	Consistent	Direct	Imprecise	Insufficient
Mania	6 months 7-12 months 12+ months	5 RCTs (n=422)	Mixed evidence with no clear direction of effect. No pattern across time periods.	High	Inconsistent	Direct	Imprecise	Insufficient
Global Function	6 months 12 months	3 RCTs (n=269)	No difference between groups at 6 or 12 months.	Moderate	Consistent	Direct	Imprecise	Insufficient
Other Measures of Function	6 months 7-12 months 12+ months	2 RCTs (n=119)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient

Abbreviations: RCT=randomized controlled trial

Appendix Table J5. Characteristics of eligible studies: psychoeducation vs. active comparators by year then first author

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Bilderbeck, 2016 ¹² RCT United Kingdom Government Moderate 27454410	N =121 Age 44 (16-76) Female 73% White 93% BP I 65% BP II 35% Outpatient	Maintenance; Individuals with BP I or II (DSM-IV) but not in a current mood episode and without a need for acute treatment Labs/Other Conditions	Therapist facilitated psychoeducation via manual focused on identifying the relapse, reviewing risk factors, daily sleep regulation, medications and substance abuse; and mood management planning. -5 face to face sessions over 12 weeks	Self-administered psychoeducation via manual focused on identifying the relapse, reviewing risk factors, daily sleep regulation, medications and substance abuse; and mood management planning. -Manual access for 12 weeks	12 months	Relapse (Intervention for emergent mood symptoms and/or admission to inpatient care or intensive community treatment) Hospitalization QIDS-SR16 ASRM Withdrawal 31%
Kallestad, 2016 ¹³ RCT Norway NR High 27253214	N = 85 Age 38 (19-64) Female 54% Race NR BP I 47% BP II 53% Outpatient	No current clinical state excluded; Individuals with BP I or II (DSM-IV) without an elevated risk of suicide Labs/Other Conditions; Neurological Disorders	Group psychoeducation focused on illness education, symptoms, early detection, sleep, risk factors, stress management, causes, work, social rights/welfare system and law/regulations -Ten initial 90-minute sessions and 8 booster sessions over next 2 years at 3-month intervals	Individual psychoeducation focused on treatment, stress management, sleep, dysfunctional cognitions, and other psychosocial factors associated with increased risk of relapse -Three 1-hour weekly sessions	27 months	Hospitalizations Time to First Admission Withdrawal 11%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Morriss, 2016 ¹⁴ RCT United Kingdom Government Moderate 27688021	N = 304 Age 45 (33-57) Female 58% Race NR BP I 80% BP II 20% Outpatient	Maintenance; Individuals with BP I or II (DSM-IV) with no current episode, but with an increased risk of relapse (occurrence of at least one episode in the past 24 months). Labs/Other Conditions; Other Mental Health	Structured group psychoeducation focused on life charting, recognition of early warning signs, problem solving, sleep hygiene, and care planning -21 weekly sessions for 2 hours each over a maximum of 26 weeks.	Optimized unstructured group support where participants set the agenda at each meeting -21 weekly sessions for 2 hours each over a maximum of 26 weeks	96 weeks	Relapse (LIFE, DSM- IV) Time to relapse HAM-D MAS SOFAS SAS Withdrawal 33%

Abbreviations: BP=bipolar disorder; BRMS= Bech-Rafaelsen Mania Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAF=General Assessment of Functioning Scale; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HDRS= Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MINI=MINI International Neuropsychiatric Interview; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; SPS=Social Phobia Scale; WHO-QOL-bref= World Health Organization Quality of Life-short version; YMRS = Young Mania Rating Scale

Appendix Table J6. Summary risk of bias assessments: psychoeducation vs. active comparators by year then first author

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Bilderbeck, 2016 ¹² Government 27454410	Moderate	Suspected bias due to possible selective reporting of outcome data (only summary statistics reported).
Kallestad, 2016 ¹³ NR 27253214	High	Suspected bias due to unclear reporting of loss of follow-up and results.
Morriss, 2016 ¹⁴ RCT Government 27688021	Moderate	Suspected bias due to attrition rate (33%) and unclear reporting of loss to follow-up.

Abbreviations: PMID=PubMed Identification Number

Appendix Table J7. Outcomes summary: psychoeducation vs. active comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Bilderbeck, 2016 ¹² 27454410	<u>Relapse</u> 12 months NS; p>0.10 N=88 Therapist-Administered Psychoeducation=25 Self-Administered Psychoeducation=25	<u>Depression</u> 12 months, QIDS-SR16 NS Adjusted Mean Difference=0.17 (95% CI - 1.35, 1.69); p=0.83 <u>Mania</u> 12 months, ASRM (Score >5) NS OR=0.71 (95% CI 0.35, 1.41); p=0.32	NR	<u>Hospitalizations</u> 12 months NS Therapist-Administered Psychoeducation=6 Self-Administered Psychoeducation=6	NR
Kallestad, 2016 ¹³ 27253214				<u>Hospitalizations</u> 27 months Group Psychoeducation: 581.% Individual Psychoeducation: 40.4% <u>Time to First Admission</u> 27 months Favors Group Psychoeducation p<0.01	
Morriss, 2016 ¹⁴ 27688021	<u>Relapse*</u> 96 weeks, Any Type NS OR=0.75 (95% CI 0.46, 1.23)' p=0.24 <u>Time to Relapse</u> 96 weeks NS HR=0.83 (95% CI 0.62, 1.11); p=0.22	<u>Mania*</u> 96 weeks, MAS* NS ES=0.01 (95% CI -0.26, 0.28) <u>Depression*</u> 96 weeks, HAM-D NS ES=-0.10 (95% CI -0.38, 0.17)	<u>Social and Occupational Functioning*</u> 96 weeks, SOFAS NS ES=0.16 (95% CI -0.11, 0.44) <u>Social Functioning*</u> 96 weeks, SAS NS ES=-0.26 (95% CI -0.54, 0.01)	NR	NR

Abbreviations: AE=Adverse Events; BRMS=Bech-Rafaelsen Mania Scale; CI=Confidence Interval; ES=Effect Size; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HDRS=Hamilton Depression Rating Scale; HR=Hazard Ratio; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported;

NS=not significant; OR= Odds Ratio; PMID=PubMed Identification Number; SPS=Social Phobia Scale; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table J8. Summary of strength of evidence: Psychoeducation vs. active comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	12+ months	2 RCTs (n=425)	No difference between groups for two different outcome time periods (12 months and 96 weeks). One RCT compares psychoeducation formats.	Moderate	Consistent	Direct	Impercise	Insufficient
Depression	12+ months	2 RCTs (n=425)	No difference between groups for two different outcome time periods (12 months and 96 weeks). One RCT compares psychoeducation formats.	Moderate	Consistent	Direct	Impercise	Insufficient
Mania	12+ months	2 RCTs (n=425)	No difference between groups for two different outcome time periods (12 months and 96 weeks). One RCT compares psychoeducation formats.	Moderate	Consistent	Direct	Impercise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	96 weeks	1 RCT (n=121)	No difference between groups in two measures of function at 96 weeks.	Hgh	Unclear	Direct	Impercise	Insufficient

Abbreviations: RCT=randomized controlled trial

References for Appendix J

1. Barnes CW, Hadzi-Pavlovic D, Wilhelm K, et al. A web-based preventive intervention program for bipolar disorder: outcome of a 12-months randomized controlled trial. *Journal of Affective Disorders*. 2015 Mar 15;174:485-92. doi: <http://dx.doi.org/10.1016/j.jad.2014.11.038>. PMID: 25554993.
2. Gumus F, Buzlu S, Cakir S. Effectiveness of individual psychoeducation on recurrence in bipolar disorder; a controlled study. *Archives of psychiatric nursing*. 2015 01 Jun;29(3):174-9. doi: <http://dx.doi.org/10.1016/j.apnu.2015.01.005>. PMID: 26001717.
3. de Barros Pellegrinelli K, de OCLF, Silval KI, et al. Efficacy of psychoeducation on symptomatic and functional recovery in bipolar disorder. *Acta Psychiatrica Scandinavica*. 2013 Feb;127(2):153-8. doi: <http://dx.doi.org/10.1111/acps.12007>. PMID: 22943487.
4. Javadpour A, Hedayati A, Dehbozorgi GR, et al. The impact of a simple individual psychoeducation program on quality of life, rate of relapse and medication adherence in bipolar disorder patients. *Asian Journal of Psychiatry*. 2013 Jun;6(3):208-13. doi: <http://dx.doi.org/10.1016/j.ajp.2012.12.005>. PMID: 23642977.
5. Smith DJ, Griffiths E, Poole R, et al. Beating Bipolar: exploratory trial of a novel Internet-based psychoeducational treatment for bipolar disorder. *Bipolar Disorders*. 2011 Aug-Sep;13(5-6):571-7. doi: <http://dx.doi.org/10.1111/j.1399-5618.2011.00949.x>. PMID: 22017225.
6. Sajatovic M, Davies MA, Ganocy SJ, et al. A comparison of the life goals program and treatment as usual for individuals with bipolar disorder. *Psychiatric Services*. 2009 Sep;60(9):1182-9. doi: <http://dx.doi.org/10.1176/appi.ps.60.9.1182>. PMID: 19723732.
7. Colom F, Vieta E, Sanchez-Moreno J, et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial.[Erratum appears in Br J Psychiatry. 2009 Jun;194(6):571]. *British Journal of Psychiatry*. 2009 Mar;194(3):260-5. doi: <http://dx.doi.org/10.1192/bjp.bp.107.040485>. PMID: 19252157.
8. Colom F, Vieta E, Martinez-Aran A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of General Psychiatry*. 2003 Apr;60(4):402-7. PMID: 12695318.
9. Colom F, Vieta E, Reinares M, et al. Psychoeducation efficacy in bipolar disorders: beyond compliance enhancement. *Journal of Clinical Psychiatry*. 2003 Sep;64(9):1101-5. PMID: 14628987.
10. Weiss RD, Griffin ML, Greenfield SF, et al. Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. *Journal of Clinical Psychiatry*. 2000 May;61(5):361-7. PMID: 10847311.
11. Perry A, Tarrier N, Morriss R, et al. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *BMJ*. 1999 Jan 16;318(7177):149-53. PMID: 9888904.
12. Bilderbeck AC, Atkinson LZ, McMahon HC, et al. Psychoeducation and online mood tracking for patients with bipolar disorder: A randomised controlled trial. *Journal of Affective Disorders*. 2016 15 Nov;205:245-51. doi: <http://dx.doi.org/10.1016/j.jad.2016.06.064>. PMID: 27454410 PMID/612460558 Embase.
13. Kallestad H, Wullum E, Scott J, et al. The long-term outcomes of an effectiveness trial of group versus individual psychoeducation for bipolar disorders. *Journal of Affective Disorders*. 2016;202:32-8. doi: <http://dx.doi.org/10.1016/j.jad.2016.05.043>. PMID: 27253214 PMID/611342382 Embase.
14. Morriss R, Lobban F, Riste L, et al. Clinical effectiveness and acceptability of structured group psychoeducation versus optimised unstructured peer support for patients with remitted bipolar disorder (PARADES): a pragmatic, multicentre, observer-blind, randomised controlled superiority trial. *The Lancet Psychiatry*. 2016 01 Nov;3(11):1029-38. doi: <http://dx.doi.org/10.1016/S2215-0366%2816%2930302-9>. PMID: 27688021.

Appendix K. Cognitive Behavioral Therapy

Appendix Table K1. Characteristics of eligible studies: CBT vs. inactive comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Jones, 2015 ¹ RCT United Kingdom Government Moderate 25213157	N = 67 39 (18-65) Female 70% White 96% BP II 21% Outpatient	Euthymic/Maintenance; DSM-IV diagnosis of primary BP I or II (DSM-IV) with onset in past 5 years Schizoaffective	Individual CBT focused on recovery approach, mood functioning, understanding of diagnosis, recovery- informed goals, relationships between mood and progress towards recovery goals, CBT techniques to cope, functioning issues in relation to recovery, development of recovery plan, and sharing lessons from therapy with stakeholders -Total of 18 hours over 6 months; weekly or biweekly 45-60 minute sessions	Treatment as usual: Routine medication (mood stabilizers, antipsychotics, and antidepressants) and medical care from clinician and community mental health team.	12 months 15 months (Relapse Only)	PSP QoL.BD BDI-II Relapse (SCID-LIFE, HRSD, MAS) Time to Recurrence 12 months: 33% 15 months: 54%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Perich, 2013 ² RCT Australia Government and Non-Government Moderate 23216045	N=95 Age NR (18+) Female 65% White NR BP I 62% BP I 37% BP NOS 1% Outpatient	Euthymic/Maintenance; BP I or II (DSM-IV), on a mood stabilizing medication for the duration of study treatment with at least one bipolar disorder episode (hypo/mania, depression, mixed episode) over the previous 18 months; and a lifetime incidence of at least three bipolar episodes Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Labs/Other Conditions	Group mindfulness- based CBT consisting of mindfulness meditation practice and cognitive therapy regarding depression including psycho- education (education about bipolar disorder, depression, hypo/mania, and anxiety). -8 weekly sessions, each 2 to 2.5 hours	Treatment as usual: Weekly handouts with information about bipolar disorder via email or mail. Topics included causes of bipolar disorder, available treatments, and common symptoms.	12 months	MADRS YMRS Relapse (DSM-IV major depressive, hypomanic or manic episode) 38%
Fava, 2011 ³ RCT Italy Government and Non- Government Low 21372621	N = 62 Age 40 (18-65) Female 55% White NR Cyclothymic 100% Outpatient	No history of mania or major depressive disorder; Current diagnosis of cyclothymic disorder according to DSM-IV First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Medications; Pregnant/Nursing; Labs/Other Conditions	CBT and well-being therapy focused on patient's symptomatology, monitoring of distress, strategies for symptom management, psychotherapeutic strategy for enhancing well- being -10 sessions every other week for 45- minutes.	Clinical Management: Reviewed the patient's clinical status and provided the patient with support and advice according to protocol -10 sessions every other week for 45- minutes.	24 months	CID MAS 18%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Gomes, 2011 ⁴ RCT Brazil Government and Non- Government High 21372622	N = 50 Age 39 (18-60) Female 76% White NR BP I 76% BP II 24% Outpatient	Euthymic/Maintenance; BP I or II (DSM-IV) with more than 5 years of schooling, and use of at least one mood stabilizer or atypical antipsychotic YMRS <6 HDRS <8 Substance Abuse; Neurological Disorders	Group CBT focused on information about BP and stabilized routine and pharmacological issues; use of mood graphs and stress vulnerability model, cognitive and behavioral strategies to manage depressive and manic episodes; specific problems in BP; techniques to improve relapse prevention -18 structured sessions, 90 minutes each	Treatment as usual: Pharmacological treatment	24 months	Relapse (Not Defined) Time to relapse 6%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Castle, 2010 ⁵ RCT Australia Government and Non- government Low 20435965	N = 84 Age 42 (18-65) Female 76% White NR BP I 74% BP II 25% BP NOS 1% Outpatient	Euthymic/Maintenance; BP I, BP II, or BP NOS (DSM- IV); not in an acute episode as defined by DSM-IV criteria Schizoaffective; Neurological Disorders; Labs/Other Conditions	Group CBT focused on monitoring mood and activities, assessing prodromes, preventing relapse, and setting specific, measurable, achievable, realistic, time-framed goals -12 weekly group sessions (90 minutes) and 3 monthly booster sessions with weekly telephone calls	Treatment as usual (not defined) and weekly telephone call	12 months	Relapse (DSM-IV-TR criteria for any mood episode) MADRS YMRS 14%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Ball, 2006 ⁶ RCT Australia Non-government and industry High 16566624	N = 52 Age 42 (23-77) Female 58% White NR BP NR Outpatient	Without current episode of severe depression or mania; BP I or BP II (DSM- IV) with at least 1 episode of hypomania, mania, or depression over prior 18 months; able to maintain usual mood stabilizing medications for duration of treatment. BDI<30 HAM-D-17 <15 YMRS<20 Schizoaffective; Other Mental Health; Neurological Disorders; Labs/Other Conditions	CBT focused on assessment, psychoeducation, identifying early warning signs, establishing stable routines, identifying and modifying cognitions, identifying and modifying schemas -20 weekly sessions, 60 minutes each	Treatment as usual: Regular sessions as prescribed by patient's medical practitioner	12 months	Relapse (DSM-IV hypo/manic, depressive, or mixed episodes at least 2 months after symptomatic remission) MADRS YMRS GAF SAS ATQ-N WHO-DAS 37%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Scott, 2006 ⁷ RCT United Kingdom Government Low/High 16582056	N = 253 Age 41 (18-65) Female 65% White NR BP I 94% BP II 6% Outpatient	Depressed, Hypo/ manic, or Euthymic; BP I or BP II (DSM-IV) with history of two or more episodes of illness meeting DSM-IV criteria for mania, hypomania, major depressive disorder or mixed affective disorder, one of which must have been within 12 months of recruitment; and contact with mental health services within the past 6 months. First Manic Episode; Substance Abuse; Other Mental Health; Neurological Disorders	CBT focused on facilitating acceptance of the need for treatment, reducing variability in mood, managing stressors, strategies to cope with depression, identifying and modifying dysfunctional automatic thoughts and beliefs, improve medication adherence, tackling substance misuse, teaching early recognition of symptoms of recurrence and coping techniques for symptoms -Weekly sessions for 15 weeks with reduction in frequency from week 16-26. Two booster sessions week at 32 and 38.	Treatment as usual: Medication and contact with key mental health professionals when appropriate.	18 months	Relapse LIFE-II, Depression LIFE-II, Mania 26%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Lam, 2003, 2005 ^{8,9} RCT England NR Low Moderate 12578431 15677598	N = 103 Age 44 (22-70) Female 56% White NR BP I 100% Outpatient	Euthymic/Maintenance; BP I (DSM-IV) with prescribed prophylactic medication at an adequate dose according to the British National Formulary, with at least 2 episodes in the last 2 years or 3 episodes in the last 5 years, but currently not fulfilling criteria for a bipolar episode; BDI <30 BRMS<9 First Manic Episode; Schizoaffective; Substance Abuse; Other Mental Health	CBT focused on traditional cognitive therapy for depression, diathesis-stress model and need for pharmaceutical and psychological therapy, mood monitoring and prodromes, sleep importance, and targeting extreme striving attitudes and behavior -12 to 18 individual 60-minute sessions in the first 6 months and 2 booster sessions in the second 6 months.	Minimal psychiatric care: Mood stabilizers (at appropriate level) and regular outpatient psychiatric follow up	12 months 2.5 years	Relapse (DSM-IV criteria for any bipolar episode) HDRS BRMS SPS Hospitalizations 16%

Abbreviations: BDI=Beck Depression inventory; BP=bipolar disorder; BRMS=Bech-Rafaelsen Mania Scale; CBT=Cognitive Behavioral Therapy; CID=Clinical Interview for Depression; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAF=General Assessment of Functioning Scale; HAM-D=Hamilton Scale for Depression; HDRS=Hamilton Depression Rating Scale; LIFE=Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; MAS=Bech-Rafaelsen Mania Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; PSP=Personal and Social Functioning Scale; QoL.BD=Quality of Life; RCT=randomized controlled trial; SCID=Structured Clinical Interviews for DSM Disorders; SPS=Social Phobia Scale; YMRS=Young Mania Rating Scale

Appendix Table K2. Summary risk of bias assessments: CBT vs. inactive comparators

Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Jones 2015 ¹ Government 25213157	Moderate	Potential bias due to rate of attrition at 12 months (~33%) and differential rate of attrition between study arms.
Perich 2013 ² Government and Non-government 23216045	Moderate	Potential reporting bias due to unclear reporting of sample sizes by arm. Almost 40% lost to follow up at outcome time points.
Fava 2011 ³ Government and Non-government 21372621	Low	No significant suspected biases.
Gomes 2011 ⁴ Government and Non-government 21372622	High	Suspected bias due to attrition post-randomization in treatment arm with high differential attrition between groups.
Castle 2010 ⁵ Government and Non-government 20435965	Low	No significant suspected biases.
Ball 2006 ⁶ Non-government and Industry 16566624	High	Suspected bias due to unclear reporting of reasons for withdrawal by treatment arm. High differential attrition between groups.
Scott 2006 ⁷ Government 16582056	Low/High (Post-hoc analysis)	No significant suspected biases related to pre-specified outcomes; however, there is a risk of bias due to post-hoc analysis results.
Lam 2003 ⁸ NR 12578431	Low/High	No significant suspected biases for relapse outcomes; but there is a risk of bias due to unclear reporting of symptom scores and time points.
Lam 2005 ⁹ NR 15677598	Moderate	Suspected bias due to unclear reporting of attrition and sample size by arm.

Abbreviations: NR=not reported; PMID=PubMed Identification Number

Appendix Table K3. Outcomes summary: CBT vs. inactive comparators

Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Jones, 2015 ¹ Moderate 25213158	<u>Relapse*</u> NS 15 months, Any type OR= 0.32 (95% CI 0.09, 1.06); p=0.06 <u>Time to First Recurrence</u> Favors CBT HR=0.38 (95% CI 0.18, 0.78)	<u>Depression*</u> NS 6 months, BDI ES=0.00 (95% CI -0.58, 0.58) 12 months, BDI ES=0.02 (95% CI -0.63, 0.68)	<u>Quality of Life*</u> NS 6 months, QoL.BD ES= -0.36 (95% CI -0.93, 0.22) 12 months, QoL.BD ES= -0.35 (95% CI -1.01, 0.31) <u>Social Function*</u> NS 6 months, PSP ES= -0.38 (95% CI -1.00, 0.25) 12 months, PSP ES= -0.35 (95% CI -0.75, 0.60)	NR	NR
Perich, 2013 ² Moderate 23216045	<u>Relapse*</u> NS 12 months, Depression OR= 0.67 (95% CI 0.19, 2.24); p=0.59 12 months, Hypo/manic OR= 1.90 (95% CI 0.59, 6.20); p=0.29	<u>Depression*</u> NS 6 months, MADRS ES= 0.05 (95% CI -0.35, 0.46) 12 months, MADRS ES= 0.23 (95% CI -0.18, 0.63) <u>Mania*</u> NS 6 months, YMRS ES= -0.27 (95% CI -0.67, 0.13) 12 months, YMRS ES= 0.06 (95% CI -0.34, 0.46)	NR	NR	NR

Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Fava, 2011 ³ Low 21372621	NR	<u>Depression*</u> Favors CBT 6 months, CID ES= -0.67(95% CI -1.18, -0.15) 12 months, CID ES= -0.57 (95% CI -1.08, -0.06) <u>Mania*</u> Favors CBT 6 months, BRMS ES= -0.74 (95% CI -1.25, -0.22) 12 months, BRMS ES= -0.94 (95% CI -1.46, -0.41)	NR	NR	NR
Gomes, 2011 ⁴ High 21372622	<u>Relapse*</u> NS 24 months, Any type OR=0.37 (95% CI 0.37, 5.25); p=0.77 <u>Time to First Recurrence</u> Favors CBT Median: 31 weeks CBT vs. 11.5 weeks Usual care; p=0.01	NR	NR	NR	NR
Castle, 2010 ⁵ Low 20435965	<u>Relapse*</u> Favors CBT 12 months, Any type OR=0.32 (95% CI 0.10, 0.95); p=0.03	<u>Depression*</u> NS 12 months, MADRS ES=0.41 (95% CI -0.06, 0.87) <u>Mania</u> NS 12 months, YMRS ES=0.33 (95% CI -0.14, 0.80)	NR	NR	NR

Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Ball, 2006 ⁶ High 16566624	<u>Relapse*</u> NS 6 months, Any type OR=0.50 (95% CI 0.11, 2.07); p=0.36 18 months, Any type OR=0.74 (95% CI 0.22, 2.56); p=0.78	<u>Depression*</u> Favors CBT at 6 months 6 months, MADRS ES=-0.57 (95% CI -1.12, --0.01) 18 months, MADRS ES=-0.08 (95% -0.62, 0.47) <u>Mania*</u> NS 6 months, YMRS ES= -0.02 (95% CI -0.56, 0.53) 18 months, YMRS ES= -0.13 (95% -0.67, 0.42)	<u>Function*</u> NS 6 months, GAF ES=0.43 (95% CI -0.12, 0.98) 18 months, GAF ES=0.24 (95% CI -0.30, 0.79) <u>Social Function*</u> NS 6 months, SAS ES=-0.48 (95% CI -1.03, 0.08) 18 months, SAS ES=-0.17 (95% -0.71, 0.38) <u>Cognitive Function*</u> NS 6 months, ATQ-N ES=-0.37 (95% CI -0.91, 0.18) 18 months, ATQ-N ES=0.22 (95% CI -0.32, 0.77) <u>Health and Disability*</u> Favors Intervention 6 months, WHO-DAS ES=-0.58 (95% CI -1.13, -0.02) NS 18 months, WHO-DAS ES=-0.40 (95% CI -0.95, 0.15)	NR	NR

Study ROB PMID	Responder/Remitter	Symptom	Function	Other	AE
Scott, 2006 ⁷ 16582056	<u>Relapse*</u> NS 9 months, Any type OR=0.99 (95% CI 0.56, 1.75); p=0.97 12 months, Any type OR=0.84 (95% CI 0.50, 1.42); p=0.53	<u>Depression*</u> 18 months, LIFE-II Depression NS <u>Mania*</u> NS 18 months, LIFE-II Mania	NR	NR	NR
Lam, 2003 ⁸ 12578431	<u>Relapse*</u> Favors CBT at 18 and 30 months 6 months, Any type OR=0.39 (95% CI 0.15, 1.03); p=0.05 18 months, Any type OR= 0.26 (95% CI 0.10, 0.67); p=0.00 30 months, Any type OR=0.33 (95% CI 0.11, 0.94); p=0.02	<u>Depression*</u> NS 6 months, HDRS ES= -0.17 (95% CI -0.56, 0.22) 12 months, HDRS ES= -0.13 (95% CI -0.52, 0.26) <u>Mania*</u> NS 6 months, BRMS ES=0.00 (95% CI -0.39, 0.39) 12 months, BRMS ES= -0.32 (95% CI -0.71, 0.07)	<u>Social Function*</u> Favors CBT at 6 months 6 months, SPS ES= -0.60 (95% CI -0.99, -0.20) 12 months, SPS ES=0.00 (-0.39, 0.39)	<u>Admissions for BP</u> 12 months Favors CBT OR=0.20 (95% CI 0.06, 0.61)	NR

*=Self-calculated estimate based on reported data

Abbreviations: ATQ-N=Automatic Thoughts Questionnaire Negative Subscale; BP=Bipolar Disorder; BDI=Beck depression inventory; BRMS=Bech-Rafaelsen Mania Scale; CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; ES=Effect Size; GAF=General Assessment of Functioning Scale; HR=Hazard Ratio; LIFE=Longitudinal Interval Follow-up Evaluation; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; QoL.BD=Quality of Life; ROB=risk of bias; SAS=Simpson Angus Scale; SPS=Social Phobia Scale; WHO-DAS=World Health Organization Disability Assessment Scale; YMRS = Young Mania Rating Scale

Appendix Table K4. Summary of strength of evidence: CBT vs. inactive comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	6 months 7-12 months 12+ months	7 RCTs (n=714)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Depression	6 months 7-12 months 12+ months	7 RCTs (n=716)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Mania	6 months 7-12 months 12+ months	6 RCTs (n=649)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Global Function	6 months 12+ months	1 RCT (n=52)	No difference between groups at 6 or 18 months. 6 months. GAF ES=0.43 (95% CI - 0.12, 0.98) 18 months, GAF ES=0.24 (95% CI - 0.30, 0.79)	Moderate	Unclear	Direct	Imprecise	Insufficient
Other Measures of Function	6 months 7-12 months 12+ months	3 RCTs (n=289)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient

Abbreviations: CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; ES=Effect Size; GAF=General Assessment of Functioning Scale; RCT=randomized controlled trial

Appendix Table K5. Characteristics of eligible studies: CBT vs. active comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Harvey, 2015 ¹⁰ RCT United States Government Moderate 25622197	N = 58 Age 37 (18-62) Female 62% White 64% BP I 100% Outpatient	No current bipolar episode; BP I(DSM-IV); interepisode defined by YMRS score <12 and an IDS-C score <24 for the past week, with general insomnia disorder (International Classification of Sleep Disorders, DSM- IV-TR criteria for primary insomnia) but without the exclusion for mental disorder, had a stable medication regimen for the past 4 weeks, had a treating psychiatrist Substance Abuse; Other Mental Health; Neurological Disorders; Pregnant/Nursing; Labs/Other Conditions	CBT for insomnia focusing on stimulus control, bed and sleep associations, regularizing sleep and wake times, sleep/circadian education, relaxing wind down, sleep- enhancing activities, and devising a wake-up routine. The module altered unhelpful beliefs about sleep, bedtime worry, rumination, and vigilance -8 weekly 50-60 minute sessions with behavioral module	Psychoeducation sessions that provided information but no facilitation or plan for behavior change. Sessions focused on mood regulation, the etiology of bipolar disorder, symptoms, prodromes, medications, substance use, diet, physical activity, stress management, relaxation, and self-esteem and sleep in a social context -8 weekly 50-60 minute sessions	6 months	Relapse (emergence of a new syndromal DSM-IV-TR bipolar episode) YMRS IDS-C SDS-Mood Q-LES-Q-SF 29%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Meyer, 2012 ¹¹ RCT Germany Non-government Low 22099722	N = 76 Age 44 (18-75) Female 50% White NR BP 79% BP II 21% Outpatient	Euthymic/Maintenance; Primary diagnosis of BP (DSM-IV), without a current major effective episode, and willingness to continue current or start medication. Schizoaffective; Substance Abuse; Other Mental Health; Neurological Disorders; Taking Other Medications	CBT focused on understanding of BP, identifying early warning symptoms, strategies for management, communication and problem solving skills -20 sessions over 9 months, 50-60 minutes each	Supportive Therapy: Client- centered focus; whatever problems the patient presented were dealt with by providing emotional support and general advice -20 sessions over 9 months, 50-60 minutes each.	24 months	Relapse (Any mood episode that fulfilled DSM-IV criteria) BDI BRMAS GAS 15%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Parikh, 2012 ¹² RCT Canada Government and Non- Government Low 22795205	N = 204 Age 40.9 (18-64) Female 58% White NR BP I 72% BP II 28% Outpatient	Euthymic/Maintenance; Age 18-64; BP I or II (DSM- IV) with at least 2 episodes of significant symptoms or full episodes within previous 3 years; no episode in month preceding randomization First Manic Episode; Substance Abuse; Other Mental Health; Neurological Disorders; Labs/Other Conditions	CBT including psychoeducation, understanding of personal warning signs for onset and action plan, and cognitive restructuring of dysfunctional thoughts and assumptions -20 individual 50- minute sessions	Group psychoeducation using Life Goals manual; focused on illness recognition, treatment approaches, and coping strategies and the creation of Personal Care Plan including action plan for both depression and mania -6 sessions, 90 minutes each session	18 months	Relapse (Not Described) LIFE Depression LIFE Mania 38%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Weiss, 2009 ¹³ RCT United States Government Low 19573999	N = 61 Age 38 (18-58) Female 41% White 91.8% BP I 79% BP II 15% BP NOS 6% Outpatient	Non-manic; Current diagnosis of BP (DSM-IV) and substance abuse other than nicotine, substance abuse within 60 days, a mood stabilizer regimen for more than 2 weeks, ability to attend group sessions and follow-up, without current mania. First Manic Episode; Schizoaffective; Other Mental Health; Labs/Other Conditions	Integrated group CBT on the cognitive-behavioral relapse prevention model which focuses on the similarities between recovery and relapse processes in bipolar disorder and substance abuse and their interaction -12 weekly 60- minute sessions	Group Drug Therapy: Substance use disorder therapy sessions that focused on facilitating abstinence, encouraging mutual support, and teaching new ways to cope with substance- related problems -12 weekly 60- minute sessions	6 months	HAM-D YMRS 19.6%
Weiss, 2007 ¹⁴ RCT United States Government and Non- Government Moderate 17202550	N = 62 Age 41.9 (22-65) Female 51.6% White 93.5% BP I 81% BP II 16% BP NOS 3% Outpatient	Maintenance; A current diagnosis of bipolar disorder (DSM-IV) and substance dependence other than nicotine; substance use within 60 days; a mood stabilizer regimen for ≥2 weeks; and age ≥18 First Manic Episode; Schizoaffective; Other Mental Health; Labs/Other Conditions	Integrated group CBT on cognitive- behavioral relapse prevention model which focuses on the similarities between recovery and relapse processes in bipolar disorder and substance abuse and their interaction -20 weekly 60- minute sessions	Group Drug Therapy: Focused on facilitating abstinence, encouraging mutual support, and teaching new ways to cope with substance- related problems -20 weekly 60- minute sessions	8 months	HAM-D YMRS 34%

Abbreviations: BDI=Beck depression inventory; BP=bipolar disorder; BRMS=Bech-Rafaelsen Mania Scale; CBT=Cognitive Behavioral Therapy; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; IDS=Inventory for Depressive Symptoms; LIFE=Longitudinal

Interval Follow-up Evaluation; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; Q-LES-Q-SF=Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form; RCT=randomized controlled trial; SDS-Mood=Sheehan Disability Scale-Mood; YMRS = Young Mania Rating Scale

Appendix Table K6. Summary risk of bias assessments: CBT vs. active comparators

Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
Harvey, 2015 ¹⁰ Government 25622197	Moderate	Potential bias due to differential attrition rates between arms.
Meyer, 2012 ¹¹ Non-government 22099722	Low	No significant suspected biases.
Parikh, 2012 ¹² Government and Non-Government 22795205	Low	No significant suspected biases.
Weiss, 2009 ¹³ Government 19573999	Low	No significant suspected biases.
Weiss, 2007 ¹⁴ Government and Non-Government 17202550	Moderate	Potential bias due to incomplete outcome reported and unclear reporting of methods for analysis of data.

Abbreviations: PMID=PubMed Identification Number

Appendix Table K7. Outcomes summary: CBT vs. active comparators

Study Risk of Bias PMID	Responder/Remitter	Symptom	Function	Other	AE
Harvey, 2015 ¹⁰ Moderate 25622197	<u>Relapse</u> 6 months, Favors CBT Hypo/manic 4.6% CBT vs. 31.6% Psychoeducation, p = .036 <u>Relapse</u> NS 6 months, Depressive 9.1% CBT vs. 21.1% Psychoeducation, p = 0.39.	<u>Depression</u> NS 6 months, IDS-C ES= -0.30; p=0.33 <u>Mania</u> NS 6 months, YMRS ES= -0.02; p=0.60	<u>Quality of Life</u> NS 6 months, Q-LES-Q-SF ES=-0.47 (95% CI - 0.99, 0.05) <u>Disability</u> NS 6 months, SDS-Mood ES=0.24 (95% CI - 0.27, 0.76)	NR	NR

Study Risk of Bias PMID	Responder/Remitter	Symptom	Function	Other	AE
Meyer, 2012 ¹¹ Low 22099722	<u>Relapse</u> NS 9 months, Any type OR=0.42 (95% CI 0.15, 1.16); p=0.10 30 months, Any type OR=1.41 (95% CI 0.50, 4.05); p=0.63	<u>Depression</u> NS 9 months, BDI No statistical test reported <u>Mania</u> NS 9 months, BRMAS ES=0.33 (95% CI -0.16, 0.82)	<u>Global Function</u> NS 9 months, GAS ES=-0.20 (95% CI -0.68, 0.29)	NR	NR
Parikh, 2012 ¹² Low 22795205	<u>Relapse</u> NS 18 months, Hypomanic/manic p=0.46 <u>Relapse</u> NS 18 months, Depressive p=0.76	<u>Depression</u> NS 18 months, LIFE Depression p=0.89 <u>Mania</u> NS 18 months, LIFE Mania p=0.96	NR	NR	NR
Weiss, 2009 ¹³ Low 19573999	NR	<u>Depression</u> NS 6 months, HAM-D No statistical test reported <u>Mania</u> NS 6 months, YMRS No statistical test reported ES=-0.54 (95% CI -1.05, -0.03)	NR	NR	NR
Weiss, 2007 ¹⁴ 17202550	NR	<u>Depression</u> NS 8 months, HRSD <u>Mania</u> NS 8 months, YMRS	NR	NR	NR

Abbreviations: BDI=Beck depression inventory; CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; ES=Effect Size; GAS=Global Assessment Scale; HAM-D=Hamilton Scale for Depression; HRSD=Hamilton Rating Scale for Depression; IDS=Inventory for Depressive Symptoms; LIFE=Longitudinal Interval Follow-up Evaluation; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; SDS-Mood=Sheehan Disability Scale-Mood; YMRS=Young Mania Rating Scale

Appendix Table K8. Summary of strength of evidence: CBT vs. active comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	6 months 7-12 months 12+ months	3 RCTs (n=338)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Depression	6 months 7-12 months 12+ months	5 RCTs (n=461)	No difference between groups across range of time periods.	Moderate	Consistent	Direct	Imprecise*	Low; No effect from intervention
Mania	6 months 7-12 months 12+ months	5 RCTs (n=461)	No difference between groups across range of time periods	Moderate	Consistent	Direct	Imprecise*	Low; No effect from intervention
Global Function	9 months	1 RCT (n=76)	No difference between groups at 9 months ES=-0.20 (95% CI -0.68, 0.29)	Low	Unclear	Direct	Imprecise	Insufficient
Other Measures of Function	6 months	1 RCT (n=58)	No difference between groups at 6 months in either QoL or disability. Q-LES-Q-SF ES=-0.47 (95% CI -0.99, 0.05) SDS-Mood ES=0.24 (95% CI - 0.27, 0.76)	Low	Unclear	Direct	Imprecise	Insufficient

*It is difficult to establish a level of precision that provides confidence of no effect. Due to the large number of comparisons with findings of no effect, we assessed strength of evidence cautiously when there was imprecision, only assigning low strength of evidence when there was sufficient sample size, low to moderate study limitations, and consistency

Abbreviations: CBT=Cognitive Behavioral Therapy; CI=Confidence Interval; ES=Effect Size; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire; RCT=randomized controlled trial; SDS-Mood=Sheehan Disability Scale-Mood

References for Appendix K

1. Jones SH, Smith G, Mulligan LD, et al. Recovery-focused cognitive-behavioural therapy for recent-onset bipolar disorder: randomised controlled pilot trial.[Erratum appears in Br J Psychiatry. 2015 Feb;206(2):169]. British Journal of Psychiatry. 2015 Jan;206(1):58-66. PMID 25213157.
2. Perich T, Manicavasagar V, Mitchell PB, et al. A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. Acta Psychiatrica Scandinavica. 2013 May;127(5):333-43. PMID 23216045.
3. Fava GA, Rafanelli C, Tomba E, et al. The sequential combination of cognitive behavioral treatment and well-being therapy in cyclothymic disorder. Psychotherapy & Psychosomatics. 2011;80(3):136-43. PMID 21372621.
4. Gomes BC, Abreu LN, Brietzke E, et al. A randomized controlled trial of cognitive behavioral group therapy for bipolar disorder. Psychotherapy & Psychosomatics. 2011;80(3):144-50. PMID 21372622.
5. Castle D, White C, Chamberlain J, et al. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. British Journal of Psychiatry. 2010 May;196(5):383-8. PMID 20435965.
6. Ball JR, Mitchell PB, Corry JC, et al. A randomized controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. Journal of Clinical Psychiatry. 2006 Feb;67(2):277-86. PMID 16566624.
7. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. British Journal of Psychiatry. 2006 Apr;188:313-20. PMID 16582056.
8. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Archives of General Psychiatry. 2003 Feb;60(2):145-52. PMID 12578431.
9. Lam DH, Hayward P, Watkins ER, et al. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. American Journal of Psychiatry. 2005 Feb;162(2):324-9. PMID 15677598.
10. Harvey AG, Soehner AM, Kaplan KA, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. J Consult Clin Psychol. 2015 Jun;83(3):564-77. PMID 25622197.
11. Meyer TD, Hautzinger M. Cognitive behaviour therapy and supportive therapy for bipolar disorders: relapse rates for treatment period and 2-year follow-up. Psychological Medicine. 2012 Jul;42(7):1429-39. PMID 22099722.
12. Parikh SV, Zaretsky A, Beaulieu S, et al. A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: a Canadian Network for Mood and Anxiety treatments (CANMAT) study [CME]. Journal of Clinical Psychiatry. 2012 Jun;73(6):803-10. PMID 22795205.
13. Weiss RD, Griffin ML, Jaffee WB, et al. A "community-friendly" version of integrated group therapy for patients with bipolar disorder and substance dependence: a randomized controlled trial. Drug & Alcohol Dependence. 2009 Oct 1;104(3):212-9. PMID 19573999.
14. Weiss RD, Griffin ML, Kolodziej ME, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. American Journal of Psychiatry. 2007 Jan;164(1):100-7. PMID 17202550.

Appendix L. Systematic or Collaborative Care

Appendix Table L1. Characteristics of eligible studies: systematic or collaborative care vs. inactive comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
van der Voort, 2015 ¹ van der Voort, 2015b ² RCT Netherlands NR Low 25792695 25841077	N=138 Age 46 (18-65) Female 64% White NR BP I 64% BP II 28% BP NOS 4% Outpatient	Maintenance; BP I, II or NOS (DSM-IV-TR) not experiencing a severe manic or depressive episode (6 or 7 on CGI BP) and stable enough to function well with only low- intensity treatment. Other Mental Health; Labs/Other Conditions	Collaborative care including formation of care team (including a family member with patient consent), formation of treatment plan with needs assessment, psychoeducation, problem solving treatment, mood charting, recognition of early warning signs and formation of relapse prevention, and pharmacotherapy and somatic care. -12 months of collaborative care	Treatment as usual (not described)	12 months	QIDS ASRM FAST-NL-P WHO-QOL-bref Withdrawal 15%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kessing, 2013 ³ RCT Denmark Non-Government Low/High 23349295	N=158 Age 37 (27-48) Female 54% White NR BP NR Outpatient	No current clinical state excluded; Individuals discharged from first, second, or third hospital admission from inpatient psychiatric hospital with diagnosis of manic episode of bipolar disorder. Neurological Disorders; Other Mental Health; Labs/Other Conditions	Specialized outpatient care including a medical evaluation, treatment plan, pharmacological treatment, group sessions consisting of psychoeducation and discussions about subjects' experiences and a discharge group focused on identifying early warning signs and communication of signs to clinicians. -Specialized care for 2 years including 12 sessions of psychoeducation (1.5 hours per session) and 3-6 months of discharge group	Treatment as usual: Standard outpatient mental health services included treatment with a general practitioner, psychiatrist, or community mental health center.	24 months	Readmissions Relapse Withdrawal 35%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kilbourne, 2012 ⁴ RCT US Government Low 23203358	N=68 Age 43 (18-71) Female 61% White 78% BP NR Outpatient	No current clinical state excluded; BP I, II or NOS with one or more cardiometabolic risk factor. Neurological Disorders; Labs/Other Conditions	Life Goals Collaborative Care consisting of weekly group self- management sessions (mixture of motivational interviewing and cognitive behavioral techniques) with care management by interventionist and providers -Four 2-hour sessions of self- management, 6 months of care management	Enhanced Treatment as Usual: Usual care and monthly mailings on mental health care and referrals to primary care services	12 months	ISS Depression ISS Mania SF-12 Mental SF-12 Physical WHO-DAS Withdrawal 4%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Kilbourne, 2008 ⁵ RCT US Government and Industry Moderate 18586993	N=61 Age 55 (39-71) Female 9% White 90% BP I 76% BP II 7% BP NOS 17% Outpatient	No current clinical state excluded; BP I, II or NOS with cardiovascular disease-related risk factor Substance Abuse; Other Mental Health; Labs/Other Conditions	Bipolar disorder medical care model consisting of self- management (adapted fro Life Goals Program) education, care management via nurse care manager who coordinated with providers regarding medical and psychiatric care, and guideline implementation training for providers -Three sessions (2 hours) of self- management program; 6 months of care management	Treatment as usual: Routine care (as selected by provider) without self- management or care management	6 months	ISS Depression ISS Mania SF-12 Mental SF-12 Physical WHO-DAS Withdrawal 5%
Bauer, 2006 ⁶ RCT US Government Low 16816277	N=330 Age 47 (26-66) Female 28% White 29% BP I 87% BP II 13% Inpatient/Outpatient	No current clinical state excluded; BP I, II or NOS (DSM-IV) identified during acute hospitalization for bipolar disorder. Neurological Disorders; Labs/Other Conditions	Bipolar Disorders Program including psychoeducation via the Life Goals Program and care team consisting of nurse care coordinator and psychiatrist -3 years of care via the program	Treatment as usual: Treatment based on psychiatrist choice	3 years	SF-36 Mental SF-36 Physical PSR Depression PSR Mania Withdrawal 7%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Simon, 2005 ⁷ Simon, 2006 ⁸ RCT US Government Low/High 15842025 16651507	N=441 Age 44 (20-68) Female 68% White 88% BP I 51% BP II 49% Outpatient	No current clinical state excluded; BP I or II (DSM- IV or treating psychiatrist) Neurological Disorders; Labs/Other Conditions	Systematic care consisting of structured initial assessment and planning, telephone monitoring, coordinated mental health treatment team, and psychoeducation. -Services offered for 24 months post- randomization	Treatment as usual: Services that are normally available without any additional care	24 months	Hospitalizations Relapse PSR Depression PSR Mania Withdrawal 6%

Abbreviations: ASRM=Altman Self-Rating Mania Scale; BP=bipolar disorder; CGI=Clinical Global Impressions; DSM=Diagnostic and Statistical Manual of Mental Disorders; FAST-NL-P=Functioning Assessment Short Test; ISS=Internal States Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; PSR=Psychiatric Status Rating; QIDS=Quick inventory of depression symptomatology; RCT=randomized controlled trial; SF-12=12-Item Short Form Health Survey; SF-36=36-Item Short Form Health Survey; WHO-DAS=World Health Organization Disability Assessment Scale; WHO-QOL-bref=World Health Organization Quality of Life-short version

Appendix Table L2. Summary risk of bias assessments: systematic or collaborative care vs. inactive comparators

Study Funding Source PMID	Overall Risk of Bias Assessment	Rationale
van der Voort, 2015 ¹ van der Voort, 2015b ² NR 25792695 25841077	Low	No significant suspected biases.
Kessing, 2013 ³ Non-Government 23349295	Low/High	No suspected risk of bias for primary outcome of hospitalizations; however suspected attrition bias for all other outcomes.
Kilbourne, 2012 ⁴ Government 23203358	Low	No significant suspected biases.
Kilbourne, 2008 ⁵ Government and Industry 18586993	Moderate	Suspected attrition bias due to attrition rate and incomplete outcome reporting.
Bauer, 2006 ⁶ Government 16816277	Low	No significant suspected biases.
Simon, 2005 ⁷ Simon, 2006 ⁸ Government 15842025 16651507	Low/High (by outcome)	Suspected biases due to reporting of primary outcome (symptom scores).

Abbreviations: NR=not reported; PMID=PubMed Identification Number

Appendix Table L3. Outcomes summary: systematic or collaborative care vs. inactive comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Van der Voort 20151, 2 25792695 25841077	NR	<p>Depression*</p> <p>6 months, QIDS NS; p=0.20</p> <p>12 months, QIDS Favors Intervention P=0.004; ES=0.40</p> <p>Mania*</p> <p>6 months, ASRM NS; p=0.30</p> <p>12 months, ASRM NS; p=0.80</p>	<p>Global Function*</p> <p>6 months, FAST-NL-P NS; p=0.06</p> <p>12 months, FAST-NL-P Favors Intervention p=0.01</p> <p>Quality of Life*</p> <p>6 months, WHO-Qol-bref NS ES=-0.20 (95% CI - 0.55, 0.15)</p> <p>12 months, WHO-Qol-bref NS ES=0.12 (95% CI - 0.23, 0.46)</p>	NR	NR
Kessing 20133 23349295	<p>Relapse*</p> <p>2 Years, Depressive NS OR=0.70 (95% CI 0.35, 1.41); p=0.33</p> <p>2 Years, Hypo/manic NS OR=1.26 (95% CI 0.63, 2.51); p=0.52</p>	NR	NR	<p>Readmissions 2-3 years Favors intervention Number of Readmissions (%) Intervention: 26 (36.1%), Comparator: 47 (54.7%)</p>	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Kilbourne 20124 23203358	NR	Depression* 6-12 months, ISS Depression NS; p=0.15 Mania* 6-12 months, ISS Mania NS; p=0.68	Mental Function* 6 months, SF-12 Mental NS ES=0.13 (95% CI - 0.36, 0.62) 12 months, SF-12 Mental NS ES=0.36 (95% CI - 0.13, 0.85) Physical Function* 6 months, SF-12 Physical NS ES=-0.10 (95% CI - 0.58, 0.39) 12 months, SF-12 Physical NS ES=0.21 (95% CI - 0.28, 0.70) Health and Disability* 6 months, WHO-DAS NS ES=-0.44 (95% CI - 0.93, 0.06) 12 months, WHO-DAS Favors Intervention ES=-0.56 (95% CI - 1.05, -0.06)	NR	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Kilbourne 20085 18586993	NR	Depression* 6 months, ISS Depression NS ES=0.00 (95% CI -0.52, 0.52) Mania* 6 months, ISS Mania NS ES=0.14 (95% CI -0.38, 0.66)	Mental Function* 6 months, SF-12 Mental NS ES=0.40 (95% CI -0.12, 0.92) Physical Function* 6 months, SF-12 Physical NS ES=0.25 (95% CI -0.27, 0.77) Health and Disability* 6 months, WHO-DAS NS ES=0.18 (95% CI -0.33, 0.70)	NR	NR
Bauer 20066 16816277	NR	Depression 3 years, PSR Depression NS; p=0.23 ES=0.17 Mania 3 years, PSR Mania NS; p=0.16 ES=0.16	Mental Function* 3 years, SF-36 Favors Intervention ES=0.51 (95% CI 0.29, 0.73) Physical Function* 3 years, SF-36 NS ES=0.08 (95% CI -0.14, 0.30)	Deaths NS 3 years Intervention: 7% Control: 5% (one suicide)	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Simon 2005, 20067, 8 15842025 16651507	Relapse* 12 months, Depressive NS OR=1.00 (95% CI 0.60, 1.67); p=1.00 12 months, Hypo/manic NS OR=0.64 (95% CI 0.39, 1.06); p=0.07	Depression 12 months, PSR Depression Favors intervention; p=0.04 24 months, PSR Depression NS; p=0.52 Mania 12 months, PSR Mania NS; 0.70 24 months, PSR Mania Favors intervention; p=0.04	NR	Hospitalizations 12 months NS; p=0.29 24 months NS; p=0.91	NR

Abbreviations: ASRM=Altman Self-Rating Mania Scale; CI=Confidence Interval; ES=effect size; FAST-NL-P=Functioning Assessment Short Test; ISS=Internal States Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; PSR= Psychiatric status rating; QIDS=Quick inventory of depression scores; SF-12=12-item Short Form Health Survey; WHO-DAS=World Health Organization Disability Assessment Scale; WHO-QOL-bref=World Health Organization Quality of Life-Short version

Appendix Table L4. Summary of strength of evidence: systematic or collaborative care vs. inactive comparators

Comparator	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	7-12 months 12+ months	2 RCTs (n=599)	No difference in outcome between groups across different time periods.	Moderate	Consistent	Direct	Imprecise *	Low; No effect from the intervention
Depression	6 months 7-12 months 12+ months	5 RCTs (n=1,038)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Mania	6 months 7-12 months 12+ months	5 RCTs (n=1,038)	No difference in outcome between groups across different time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Global Function	6 months 7-12 months	1 RCT (n=138)	Mixed evidence with no clear direction of effect. No pattern across time periods. 6 months, FAST-NL-P NS; p=0.06 12 months, FAST-NL-P Favors Intervention; p=0.01	Low	Unclear	Direct	Imprecise	Insufficient
Other Measures of Function	6 months 7-12 months	4 RCTs (n=597)	No difference in outcome between groups across different time periods.	Low	Inconsistent	Direct	Imprecise	Insufficient

* It is difficult to establish a level of precision that provides confidence of no effect. Due to the large number of comparisons with findings of no effect, we assessed strength of evidence cautiously when there was imprecision, only assigning low strength of evidence when there was sufficient sample size, low to moderate study limitations, and consistency

FAST-NL-P=Functioning Assessment Short Test; NS=not significant; RCT=randomized controlled trial

References for Appendix L

1. van der Voort TY, van Meijel B, Goossens PJ, et al. Collaborative care for patients with bipolar disorder: randomised controlled trial. *Br J Psychiatry*. 2015 Mar 19;doi: 10.1192/bjp.bp.114.152520. PMID: 25792695.
2. van der Voort TY, van Meijel B, Hoogendoorn AW, et al. Collaborative care for patients with bipolar disorder: Effects on functioning and quality of life. *J Affect Disord*. 2015 Mar 11;179(1):14-22. doi: 10.1016/j.jad.2015.03.005. PMID: 25841077.
3. Kessing LV, Hansen HV, Hvenegaard A, et al. Treatment in a specialised out-patient mood disorder clinic v. standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *British Journal of Psychiatry*. 2013 Mar;202(3):212-9. doi: <http://dx.doi.org/10.1192/bjp.bp.112.113548>. PMID: 23349295.
4. Kilbourne AM, Goodrich DE, Lai Z, et al. Life Goals Collaborative Care for patients with bipolar disorder and cardiovascular disease risk. *Psychiatric Services*. 2012 Dec;63(12):1234-8. doi: <http://dx.doi.org/10.1176/appi.ps.201100528>. PMID: 23203358.
5. Kilbourne AM, Post EP, Nosssek A, et al. Improving medical and psychiatric outcomes among individuals with bipolar disorder: a randomized controlled trial. *Psychiatric Services*. 2008 Jul;59(7):760-8. doi: <http://dx.doi.org/10.1176/appi.ps.59.7.760>. PMID: 18586993.
6. Bauer MS, McBride L, Williford WO, et al. Collaborative care for bipolar disorder: Part II. Impact on clinical outcome, function, and costs. *Psychiatric Services*. 2006 Jul;57(7):937-45. PMID: 16816277.
7. Simon GE, Ludman EJ, Unutzer J, et al. Randomized trial of a population-based care program for people with bipolar disorder. *Psychological Medicine*. 2005 Jan;35(1):13-24. PMID: 15842025.
8. Simon GE, Ludman EJ, Bauer MS, et al. Long-term effectiveness and cost of a systematic care program for bipolar disorder. *Archives of General Psychiatry*. 2006 May;63(5):500-8. PMID: 16651507.

Appendix M. Family or Partner Interventions

Appendix Table M1. Characteristics of eligible studies: family or partner interventions vs. inactive comparator

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
D'Souza, 2010 ¹ RCT Australia Non-Government Low 19428117	N=58 Age 41 (19-60) Female 52% White NR BP I 86% BP II 14% Outpatient	Euthymic/Maintenance: Recently remitted patients with a YMRS score <10 and a MADRS score <8 recruited within one month of discharge from hospital for bipolar relapse (MINI). Substance Abuse; Other Mental Health; Labs/Other Conditions	Patient/companion group psychoeducation consisting of discussion of symptoms, medications, and warning signs, and resources as well as psychotherapy -12 weekly sessions, 90 minutes each session	Treatment as usual: Community based case management involving weekly review with a mental health clinician and a monthly medical review -Weekly sessions for 45 minutes	15 months	MADRS YMRS Relapse (BP) symptoms requiring hospital admission or intensive community psychiatric intervention) Time to relapse Withdrawal 22%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Miller 2004 ² Solomon 2008 ³ Miller 2008 ⁴ RCT US Government High High Moderate 15555694 19032711 18363424	N=92 Age 39 (18-65) Female 57% White NR BP I 100% Outpatient	Current Episode: Inpatients, partial inpatients, or outpatients with BP I (DSM-III), a current episode (mania, depression, mixed) without alcohol or drug dependence within the past 12 months and living or in regular contact with a relative or significant other Substance abuse	Individual or group family therapy consisting of semi- structured family interventions. Individual therapy was based on McMaster Model of Family Function and group therapy included sessions focused on signs and symptoms, patient and family perspectives, and coping mechanisms. -6 to 10 sessions of family therapy, 50 minutes per session OR -6 weekly group sessions, 90 minutes per session	Pharmacotherapy: Mood stabilizer with other medications as necessary	28 months	Recovery (Two consecutive months with BRMS <6 and HDRS <7) Relapse (HDRS 17- item score >15 or BRMS score > 9 after recovery) Time to recurrence Hospitalizations Withdrawal 35%

Abbreviations: BP=bipolar disorder; BRMS=Bech-Rafaelsen Mania Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; HDRS=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MINI=MINI International Neuropsychiatric Interview; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; YMRS = Young Mania Rating Scale

Appendix Table M2. Summary risk of bias assessments: family or partner interventions vs. inactive comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
D'Souza, 2010 ¹ Non-Government 19428117	Low	No significant suspected biases.
Miller 2008 ⁴ Government 15555694	High	Suspected bias due to unclear reporting of randomization and attrition.
Solomon 2008 ³ Government 19032711	High	Suspected bias due to unclear reporting of randomization and attrition.
Miller 2004 ² Government 18363424	Moderate	Suspected bias due to attrition rate of 35%.

Abbreviations: PMID=PubMed Identification Number

Appendix Table M3. Outcomes summary: family or partner interventions vs. inactive comparators

Study PMID Risk of Bias	Responder/Remitter	Symptom	Function	Other	AE
D'Souza, 2010 ² 19428117 Low	<u>Relapse*</u> 15 months, Any Type Favors FPI OR=0.17 (95% CI 0.03, 0.78); p=0.02	<u>Depression*</u> 15 months, MADRS NS ES=-0.15 (95% CI -0.66, 0.37) <u>Mania*</u> 15 months, YMRS Favors FPI ES=-0.78 (95% CI -1.31, -0.24)	NR	NR	NR

Study PMID Risk of Bias	Responder/Remitter	Symptom	Function	Other	AE
Miller 20084 19032711 High Solomon 20083 18363424 Moderate Miller 20042 15555694 High	Relapse* 15 months, Any Type NS Individual Therapy OR=1.32 (95% CI 0.24, 7.34); p=0.50 Group Therapy OR=0.98 (95% CI 0.20, 4.51); p=0.62 Recovery 28 months NS; p=0.21 Number Recovered Individual Therapy: 16.0 Group Therapy: 21.0 Comparator: 16.0 Time to Recurrence 28 months NS; p=0.75 Months (Median) Individual Therapy: 6.0 Group Therapy: 8.0 Comparator: 12.0 Time to Recovery 28 months NS; p=0.55 Months (Median) Individual Therapy: 10 Group Therapy: 7 Comparator: 8	NR	NR	Hospitalizations 28 months Favors FPI; p=0.04 Number of Hospitalizations Individual Therapy: 5 Group Therapy: 1 Comparator: 6	NR

Abbreviations: CI=Confidence Interval; ES=effect size; FPI=family and partner interventions; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; YMRS = Young Mania Rating Scale

Appendix Table M4. Summary of strength of evidence: family or partner interventions vs. inactive comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	12+ months	2 RCTs (n=150)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Low	Inconsistent	Direct	Imprecise	Insufficient
Depression	12+ months	1 RCT (n=58)	No difference between groups at 15 months. MADRS ES=-0.15 (95% CI -0.66, 0.37)	Low	Unclear	Direct	Imprecise	Insufficient
Mania	12+ months	1 RCT (n=58)	Favors FPI at 15 months. YMRS ES=-0.78 (95% CI -1.31, -0.24)	Low	Unclear	Direct	Imprecise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	NR	-	-	-	-	-	-	-

Abbreviations: CI=Confidence Interval; ES=effect size; FPI=family and partner interventions; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; RCT=Randomized Control Trial; YMRS = Young Mania Rating Scale

Appendix Table M5. Characteristics of eligible studies: family or partner interventions vs. active comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Wenze, 2015 ⁵ RCT US Government and Non- Government Moderate 26117247	N=30 Age 47 (24-68) Female 50% White 90% BP I 77% BP II 13% BP NOS 10% Inpatient/Outpatient	No current clinical state excluded; Inpatients or at- risk outpatients diagnosed with BP I, II, or NOS (DSM- IV) and drug/alcohol abuse disorder (DSM-IV) with a current prescription for a mood stabilizing medication and access to a telephone Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	Integrated Treatment Adherence Program based on a cognitive behavioral approach focused on transitioning patients from acute to maintenance care using patient and family or significant other meetings in person and via telephone. -3 individual in- person sessions, 60 minutes per session; a 60 minute in- person session with family session, and 11 phone contacts held separately with subject and designated family member or significant other	Enhanced Assessment and Monitoring consisting of treatment as usual with enhanced monitoring (battery of interview-rated and self-report assessments followed by feedback letters)	6 months	QIDS-C CARS-M WHO-DAS Hospitalizations ER Visits Withdrawal 27%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Miklowitz, 2000 ⁶ Miklowitz, 2003 ⁷ RCT US Government and Non- Government Low Low 11018229 12963672	N=101 Age 36 (18-56) Female 63% White NR BP I 100% Inpatient/Outpatient	No current clinical state excluded: Inpatients with BP I (DSM-III) who had experienced a depressed, manic, or mixed episode in the past 3 months living with or having regular contact with close relatives Substance Abuse; Neurological Disorders; Labs/Other Conditions	Family-focused therapy with pharmacotherapy consisting of psychoeducation, developing communication skills, and learning a framework for defining problems and implementing solutions. -Uo to 21 family or marital sessions over 9 months, 60 minutes per session	Family education (2 sessions) and crisis management consisting of treatment as usual with emergency counseling sessions as needed and monthly telephone calls with patient	24 months	SADS-C Depression SADS-C Mania Relapse (NR) Withdrawal 22%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Rea, 2003 ⁸ RCT US Government and Non- Government Low 12795572	N=53 Age 26 (18-46) Female 57% White 60% BP I NR Inpatient/Outpatient	Manic; Inpatients with bipolar disorder (DSM-III), manic type currently taking mood-regulating medications with a close family member that could participate in intervention with patient. Substance Abuse; Labs/Other Conditions	Family-focused treatment (with medication management) consisting of psychoeducation, communication enhancement training, and problem-solving skills training -21 therapy sessions over 9 months (60 minutes per session) with 1 year of medication management	Individual treatment (with medication management) consisting of meeting a therapist to receive education about illness and symptoms, discuss problem- solving, and establishing goals. -21 therapy sessions over 9 months (30 minutes per session) with 1 year of medication management	24 months	Relapse (6 or 7 on BPRS/SADS-C core symptoms of depression, mania, or psychosis, and at least two ancillary symptoms) Withdrawal 45%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Simoneau, 1999 ⁹ RCT US Government and Non- Government Moderate 10609423	N=79 Age 34 (18-57) Female 54% White NR BP I NR Outpatient	Depressive, Manic, or Mixed Episode; Diagnosis of BP (DSM-III) in a manic, mixed, or depressed phase in the 3 months prior including month of study entry, living or in close contact with a relative for at least 1 to 3 months prior to study entry, and willing to take mood stabilizing medications Substance Abuse; Labs/Other Conditions	Family-focused therapy (with medication management) consisting of psychoeducation, communication- enhancement training, and problem-solving skills training -21 sessions over 9 months	Crisis management with naturalistic follow-up (with medication management) consisting of two sessions of home-based family education, crisis intervention as needed, telephone counseling and individual support sessions as needed, and monthly contacts. -9 months of management	24 months	SADS-C Withdrawal 44%

Abbreviations: BP=bipolar disorder; BPRS=Brief Psychiatric Rating Scale; CARS-M=Clinician-Administered Rating Scale for Mania; DSM=Diagnostic and Statistical Manual of Mental Disorders; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; QIDS-C=Quick Inventory of Depression Scores; RCT=randomized controlled trial; SADS-C=Schedule for Affective Disorders and Schizophrenia-Change version; WHO-DAS=World Health Organization Disability Assessment Scale;

Appendix Table M6. Summary risk of bias assessments: family or partner interventions vs. active comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Wenze, 2015 ⁵ Government and Non-Government 26117247	Moderate	Suspected bias due to format of data reporting and incomplete reporting of outcomes.
Miklowitz, 2003 ⁷ Miklowitz, 2000 ⁶ Government and Non-Government 11018229 12963672	Low	No significant suspected biases.
Rea, 2003 ⁸ Government and Non-Government 12795572	Low	No significant suspected biases.
Simoneau, 1999 ⁹ Government and Non-Government 10609423	Moderate	Suspected bias due to differential attrition rate between study arms.

Abbreviations: PMID=PubMed Identification Number

Appendix Table M7. Outcomes summary: family or partner interventions vs. active comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Wenze 2015 ⁵ 26117247	NR	<u>Depression</u> 6 months, QIDS-C Favors FPI; p<0.05 ES=0.24 <u>Mania</u> 6 months, CARS-M Favors FPI; p<0.05 ES=0.37	<u>Health and Disability</u> 6 months, WHO-DAS Favors FPI; p<0.05 ES=0.12	<u>Re-Hospitalizations</u> 6 months NS <u>Emergency Room Visits</u> 6 months NS; p<0.10	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Miklowitz 2003 ⁷ 12963672 Miklowitz 2000 ⁶ 11018229	<u>Relapse*</u> 12 months, Any Type NS OR=0.36 (95% CI 0.11, 1.09); p=0.05 Favors FPI 24 months, Any Type OR=0.22 (95% CI 0.07, 0.66); p=0.00	<u>Depression</u> 24 months, SADS-C Depression Favors FPI; p=0.005 <u>Mania</u> 24 months, SADS-C Mania NS; p=0.06	NR	NR	NR
Rea 2003 ⁸ 12795572	<u>Relapse</u> 12 months NS; p>0.10 Family/Partner Therapy: 46% Active Comparator: 52% 1-year Post-Treatment Period (24 months) Favors FPI; p<0.05 FPI: 28% Active Comparator: 60%	NR	NR	NR	NR
Simoneau 1999 ⁹ 10609423	NR	<u>Symptoms</u> 1 year post-treatment, SADS-C Favors FPI; p<0.05	NR	NR	NR

Abbreviations: CARS-M=Clinician-Administered Rating Scale for Mania; CI=Confidence Interval; FPI=Family or Partner Intervention; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; QIDS-C=Quick Inventory of Depression Scores; SADS-C=Schedule for Affective Disorders and Schizophrenia- Change version; WHO-DAS=World Health Organization Disability Assessment Scale

Appendix Table M8. Summary of strength of evidence: family or partner interventions vs. active comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precisio n	Overall Grade/ Conclusion
Relapse	7-12 months 12+ months	2 RCTs (n=154)	No difference between groups at 12 months; however FPI groups experience fewer relapses at 24 months.	Low	Consistent	Direct	Imprecise	Insufficient

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Depression	6 months 12+ months	2 RCTS (n=131)	Favors FPI at reported time periods.	Moderate	Consistent	Direct	Imprecise	Insufficient
Mania	6 months 12+ months	2 RCTS (n=131)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Moderate	Inconsistent	Direct	Imprecise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	6 months	1 RCT (n=30)	Favors FPI at 6 months. WHO-DAS ES=0.12; p<0.05	Moderate	Unclear	Direct	Imprecise	Insufficient

Abbreviations: ES=Effect Size; FPI=Family or Partner Intervention; NR=not reported; RCT=randomized controlled trial; WHO-DAS=World Health Organization Disability Assessment Scale

References for Appendix M

1. D'Souza R, Piskulic D, Sundram S. A brief dyadic group based psychoeducation program improves relapse rates in recently remitted bipolar disorder: a pilot randomised controlled trial. *Journal of Affective Disorders*. 2010 Jan;120(1-3):272-6. doi: <http://dx.doi.org/10.1016/j.jad.2009.03.018>. PMID: 19428117.
2. Miller IW, Solomon DA, Ryan CE, et al. Does adjunctive family therapy enhance recovery from bipolar I mood episodes? *Journal of Affective Disorders*. 2004 Nov 1;82(3):431-6. PMID: 15555694.
3. Solomon DA, Keitner GI, Ryan CE, et al. Preventing recurrence of bipolar I mood episodes and hospitalizations: family psychotherapy plus pharmacotherapy versus pharmacotherapy alone. *Bipolar Disorders*. 2008 Nov;10(7):798-805. doi: <http://dx.doi.org/10.1111/j.1399-5618.2008.00624.x>. PMID: 19032711.
4. Miller IW, Keitner GI, Ryan CE, et al. Family treatment for bipolar disorder: family impairment by treatment interactions. *Journal of Clinical Psychiatry*. 2008 May;69(5):732-40. PMID: 18363424.
5. Wenze SJ, Gaudiano BA, Weinstock LM, et al. Adjunctive psychosocial intervention following Hospital discharge for Patients with bipolar disorder and comorbid substance use: A pilot randomized controlled trial. *Psychiatry Res*. 2015 Aug 30;228(3):516-25. doi: 10.1016/j.psychres.2015.06.005. PMID: 26117247.
6. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. *Biological Psychiatry*. 2000 Sep 15;48(6):582-92. PMID: 11018229.
7. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Archives of General Psychiatry*. 2003 Sep;60(9):904-12. PMID: 12963672.
8. Rea MM, Tompson MC, Miklowitz DJ, et al. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. *Journal of Consulting & Clinical Psychology*. 2003 Jun;71(3):482-92. PMID: 12795572.
9. Simoneau TL, Miklowitz DJ, Richards JA, et al. Bipolar disorder and family communication: effects of a psychoeducational treatment program. *Journal of Abnormal Psychology*. 1999 Nov;108(4):588-97. PMID: 10609423.

Appendix N. Interpersonal and Social Rhythm Therapy (IPSRT)

Appendix Table N1. Characteristics of eligible studies: IPSRT vs. inactiveComparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Maintenance Therapies in Bipolar Disorder Frank, 1997 ¹ Frank, 1999 ² Rucci, 2002 ³ Frank, 2005 ⁴ Frank, 2008 ⁵ RCT US Government High (All Publications) 9171907 10609422 16143731 18829872	N=38-175 Age 35 (18-55) Female 59% White 94% BP I 93% Inpatient/Outpatient	Depressive, Manic, or Mixed; Individuals with BP I or schizoaffective disorder, manic type, (DSM-IV) and in at least their third lifetime affective episode. Severity criteria: >15 on HDRS or >15 on BRMS Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	IPSRT (acute, maintenance, or both) focused on maintaining regular daily routines, identification and management of potential triggers and interpersonal psychotherapy. -Acute weekly treatment until remission followed by biweekly sessions for 12 weeks and monthly treatment to 24 months, 45 to 55 minutes per session	Clinical management (acute, maintenance, or both) consisting of medical management of bipolar disorder (education, review of symptoms, management of adverse effects) - Acute weekly treatment until remission followed by biweekly sessions for 12 weeks and monthly treatment to 24 months, 20 to 25 minutes per session	24 months	Risk of Recurrence Remission UCLA Social Attainment Scale HDRS BRMS Withdrawal 47%

Abbreviations: BP=bipolar disorder; BRMS=Bech-Rafaelsen Mania Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; HDRS=Hamilton Rating Scale for Depression; IPSRT=Interpersonal and Social Rhythm Therapy; NOS=not otherwise specified; PMID=PubMed Identification Number; RCT=randomized controlled trial;

Appendix Table N2. Summary risk of bias assessments: IPSRT vs. inactive comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Frank, 1997 ¹ Frank, 1999 ² Rucci, 2002 ³ Frank, 2005 ⁴ Frank, 2008 ⁵ Government 9171907 10609422 16143731 18829872	High	Suspected bias due to unclear reporting of patient flow (specifically treatment of non-responders) and unclear reporting of outcomes. Suspected bias due to high attrition rate (47%).

Abbreviations: IPSRT=Interpersonal and Social Rhythm Therapy; PMID=PubMed Identification Number

Appendix Table N3. Outcomes summary: IPSRT vs. inactive comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Frank 2008 ⁵ 18829872	<u>Risk of Recurrence</u> 12 months NS; p=0.52	<u>Depression and Mania</u> 24 months, HDRS plus BRMS NS; p=0.74	<u>Occupational Functioning</u> 24 months Favors IPSRT as acute intervention; p=0.046	<u>Suicide Attempts</u> NS (between groups) Favors Intervention (compared to rate prior to study) 24 months Base Rate: 1.05/100 patient months Acute Phase Rate: 0.31/100 patient months; p<0.02 Maintenance Phase Rate: 0.06/100 patient months; p=0.004	NR
Frank 2005 ⁴ 16143731	<u>Time to Recurrence</u> 12 months Favors IPSRT HR=0.34, p=0.01				
Rucci 2002 ³ 16143731					
Frank 1999 ² 10609422	<u>Remission</u> 24 months NS 70% IPSRT vs. 72% Comparator				

Abbreviations: AE=Adverse Events; BRMS=Bech-Rafaelsen Mania Scale; HDRS=Hamilton Depression Rating Scale; HR=Hazard Ratio; IPSRT=Interpersonal and Social Rhythm Therapy; NR=not reported; NS=not significant; PMID=PubMed Identification Number

Appendix Table N4. Summary of strength of evidence: IPSRT vs. inactive comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	12 months	1 RCT (n=82)	No difference between groups at 24 months in risk of recurrence; p=0.52	High	Unclear	Direct	Imprecise	Insufficient
Depression	24 months	1 RCT (n=175)	No difference between groups, at 24 months HDRS and BRMS; p=0.74	High	Unclear	Direct	Imprecise	Insufficient
Mania	24 months	1 RCT (n=175)	No difference between groups, at 24 months HDRS and BRMS; p=0.74	High	Unclear	Direct	Imprecise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	24 months	1 RCT (n=125)	Favors IPSRT as acute intervention at 24 months Occupational Functioning; p=0.046	High	Unclear	Direct	Imprecise	Insufficient

Abbreviations: BRMS=Bech-Rafaelsen Mania Scale; HDRS=Hamilton Depression Rating Scale; IPSRT=Interpersonal and Social Rhythm Therapy; NR=not reported; RCT=randomized controlled trial

Appendix Table N5. Characteristics of eligible studies: IPSRT vs. active comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Inder, 2016 ⁶ Inder, 2015 ⁷ New Zealand Government Low Low 25346391 26698820	N=100 Age 27 (15-36) Female 76% White NR BP I 78% BP II 17% BP NOS 5% Outpatient	No current clinical state excluded; Individuals with BP I, II, or NOS (DSM-IV) Substance Abuse	IPSRT consisting of interpersonal psychotherapy with a focus on social routines and achieve of goals. -Weekly sessions for 3 months, fortnightly for up to 6 months, and then fortnightly to monthly from 6 to 18 months (frequency tailored to patient needs)	Specialist supportive care consisting of supportive psychotherapy and psychoeducation -Weekly sessions for 3 months, fortnightly for up to 6 months, and then fortnightly to monthly from 6 to 18 months (frequency tailored to patient needs)	78 weeks	LIFE Depression LIFE Mania SAS Withdrawal 16%

Abbreviations: BP=bipolar disorder; DSM-IV= Diagnostic and statistical manual, 4th edition; IPSRT=Interpersonal and Social Rhythm Therapy; LIFE=Longitudinal Interval Follow-up Evaluation; NOS=not otherwise specified; PMID=PubMed Identification Number; SAS=Simpson Angus Scale

Appendix Table N6. Summary risk of bias assessments: IPSRT vs. active comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Inder, 2016 ⁶ Inder, 2015 ⁷ Government 25346391 26698820	Low	No significant suspected biases.

Abbreviations: IPSRT=Interpersonal and Social Rhythm Therapy; PMID=PubMed Identification Number

Appendix Table N7. Outcomes summary: IPSRT vs. active comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Inder 2016 ⁶ Inder 2015 ⁷	NR	<u>Depression</u> 6 months, LIFE Depression NS 1.9 (95% CI 1.8–2.2) IPSRT vs. 1.8 (95% CI 1.6–2.0) Active Comparator; p=0.25 <u>Mania</u> 6 months, LIFE Mania NS 1.3 (95% CI 1.2–1.4) IPSRT vs. 1.3 (95% CI 1.2–1.4) Active Comparator; p=0.64	<u>Social Function</u> 6 months, SAS NS 2.0 (95% CI 1.9–2.1) IPSRT vs. 1.9 (95% CI 1.9–2.0) Active Comparator; p=0.10	<u>Suicide Attempts and Other Self-Harm</u> Unclear At 78 weeks there were reductions in attempts from baseline rate, difference between groups NR Baseline Suicide Attempts: 11% 78 Week Suicide Attempts: 1% Baseline Self-Harm Attempts: 15% 78 Week Self-Harm Attempts: 7%	NR

Abbreviations: AE=Adverse Events; CI=Confidence Interval; IPSRT=Interpersonal and Social Rhythm Therapy; LIFE=Longitudinal Interval Follow-up Evaluation; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SAS=Simpson Angus Scale

Appendix Table N8. Summary of strength of evidence: IPSRT vs. active comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	NR	-	-	-	-	-	-	-
Depression	6 months	1 RCT (n=100)	No difference between groups at 6 months. LIFE Depression 1.9 (95% CI 1.8– 2.2) IPSRT vs. 1.8 (95% CI 1.6–2.0) Active Comparator; p=0.25	Low	Unclear	Direct	Imprecise	Insufficient
Mania	6 months	1 RCT (n=100)	No difference between groups at 6 months. LIFE Mania 1.3 (95% CI 1.2– 1.4) IPSRT vs. 1.3 (95% CI 1.2–1.4) Active Comparator; p=0.64	Low	Unclear	Direct	Imprecise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	6 months	1 RCT (n=100)	No difference between groups at 6 months. SAS 2.0 (95% CI 1.9– 2.1) IPSRT vs. 1.9 (95% CI 1.9–2.0) Active Comparator; p=0.10	Low	Unclear	Direct	Imprecise	Insufficient

Abbreviations: CI=Confidence Interval; IPSRT=Interpersonal and Social Rhythm Therapy; LIFE=Longitudinal Interval Follow-up Evaluation; NR=not reported; RCT=randomized controlled trial; SAS=Simpson Angus Scale

References for Appendix N

1. Frank E, Hlastala S, Ritenour A, et al. Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. *Biological Psychiatry*. 1997 Jun 15;41(12):1165-73. PMID: 9171907.
2. Frank E, Swartz HA, Mallinger AG, et al. Adjunctive psychotherapy for bipolar disorder: effects of changing treatment modality. *Journal of Abnormal Psychology*. 1999 Nov;108(4):579-87. PMID: 10609422.
3. Rucci P, Frank E, Kostelnik B, et al. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. *American Journal of Psychiatry*. 2002 Jul;159(7):1160-4. PMID: 12091194.
4. Frank E, Kupfer DJ, Thase ME, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Archives of General Psychiatry*. 2005 Sep;62(9):996-1004. PMID: 16143731.
5. Frank E, Soreca I, Swartz HA, et al. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. *American Journal of Psychiatry*. 2008 Dec;165(12):1559-65. doi: <http://dx.doi.org/10.1176/appi.ajp.2008.07121953>. PMID: 18829872.
6. Inder ML, Crowe MT, Luty SE, et al. Prospective rates of suicide attempts and nonsuicidal self-injury by young people with bipolar disorder participating in a psychotherapy study. *Australian & New Zealand Journal of Psychiatry*. 2016 Feb;50(2):167-73. doi: <http://dx.doi.org/10.1177/0004867415622268>. PMID: 26698820.
7. Inder ML, Crowe MT, Luty SE, et al. Randomized, controlled trial of Interpersonal and Social Rhythm Therapy for young people with bipolar disorder. *Bipolar Disord*. 2015 Mar;17(2):128-38. doi: 10.1111/bdi.12273. PMID: 25346391.

Appendix O. Combination Interventions

Appendix Table O1. Characteristics of eligible studies: combination interventions vs. inactive comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Gonzalez-Isasi, 2014 ¹ Gonzalez-Isasi, 2010 ² RCT Spain Non-Government Low 20444503 23276524	N=40 Mean Age 41 (18-63) Female 48% White NR BP NR Outpatient	Euthymic or Subsyndromal; BP I or II (DSM-IV) for at least 2 years, history of severe or unfavorable progression of disease, euthymic or subsyndromal symptoms (BDI>7; YMRS> 6), not receiving any psychotherapy Labs/Other Conditions	Group psychoeducation and CBT consisting of sessions about their disorder, the relationship between thoughts and feelings, anxiety control techniques, cognitive re- structuring, problem-solving and self-esteem, and social skills. -20 weekly sessions, 90 minutes each	Standard pharmacologic treatment (mood stabilizers, antipsychotics, and/or benzodiazepines) adjusted by psychiatrist	5 years	BDI YMRS Hospitalizations Withdrawal 5%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Todd, 2014 ³ RCT UK Government and Non- Government Moderate 25129531	N=122 Age 43 (21-65) Female 72% White 89% BP I 70% BP II 25% Rapid Cycling 5% Outpatient	No current clinical state excluded: Self-reported BP I or II and scoring above a threshold for BP I or II on the MDQ None	Interactive, online recovery informed self-management intervention (Living with Bipolar) based on both psychoeducation and CBT. Ten interactive modules to help subjects learn more about bipolar experiences, increase self-esteem and self- efficacy for managing bipolar, increase ability to self- manage, and develop interpersonal skills. Modules included case studies and mood checking tools. -Access to program for 6 months	Wait list control receiving treatment as usual (general practitioner and/or specialist mental health services).	6 months	ISS Depression QoL.BD-Brief WHO-QOL-bref SASS Withdrawal 25%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Miklowitz 2003 ⁴ Cohort US Government and Non- Government High 12963672	N=100 Age 36 (18-55) Female 60% White 89% BP NR Outpatient	No current clinical state excluded; BP I or II (DSM-IV) with a hypo/manic, depressed, or mixed episode within the last 3 months, willingness to be on maintained drug regimen, living with or in regular contact with close relatives Substance Abuse; Neurological Disorders	Individual IPSRT and family (or partner) therapy. Individual IPSRT consisted of identifying interpersonal problems, using Social Rhythm Metric form, managing symptoms and identifying triggers, and relapse prevention. Family therapy involved education about BP, identification of triggers, communication enhancement, and problem- solving. -25 sessions of individual therapy and 25 sessions of family-focused therapy (frequency adapted to patient needs)	Treatment as usual: Crisis management (not described, comparison group from previous clinical trial)	12 months	Relapse SADS-C Depression SADS-C Mania Time to Recurrence Withdrawal 28%

Abbreviations: BDI=Beck depression inventory; BP=bipolar disorder; DSM-IV= Diagnostic and statistical manual, 4th edition; ISS=Internal States Scale; MDQ=Mood Disorder Questionnaire; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; QoL.BD-Brief=Quality of Life,Bipolar Disorder; RCT=randomized controlled trial; SADS-C= Schedule for Affective Disorders and Schizophrenia, change version; SASS=Simpson Angus Scale score; WHO-QOL-bref=World Health Organization Quality of Life –short version; YMRS = Young Mania Rating Scale

Appendix Table O2. Summary risk of bias assessments: combination interventions vs. inactive comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Gonzalez-Isasi, 2014 ¹ Gonzalez-Isasi, 2010 ² Non-Government 20444503 23276524	Low	No significant suspected biases.
Todd, 2014 ³ Government and Non-Government 25129531	Moderate	Suspected bias due to process for selection. Participant eligibility was based self-reported diagnosis and online clinical questionnaire.
Miklowitz 2003 ⁴ Government and Non-Government 12963672	High	Suspected bias due to process for selection. Participants were not randomized to treatment or comparator arm. Data used for comparison was from a previous study.

Abbreviations: PMID=PubMed Identification Number

Appendix Table O3. Outcomes summary: combination interventions vs. inactive comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
<p>Gonzalez-Isasi 2010² 20444503</p> <p>Gonzalez-Isasi 2014¹ 23276524</p>	NR	<p><u>Depression*</u> 11 months, BDI Favors combination intervention ES=-0.83 (95% CI -1.47, -0.18)</p> <p>17 months, BDI Favors combination intervention ES=-1.21 (95% CI -1.89, -0.53)</p> <p>5 years, BDI Favors combination intervention ES=-2.17 (95% CI -2.95, -1.37)</p> <p><u>Mania*</u> 11 months, YMRS Favors combination intervention ES=-1.0 (95% CI -1.60, -0.30)</p> <p>17 months, YMRS Favors combination intervention ES=-1.5 (95% CI -2.2, -0.80)</p> <p>5 years, YMRS Favors combination intervention ES=-1.10 (95% CI -1.80, -0.40)</p>	NR	<p><u>Hospitalizations</u> Significant difference between groups at 17- months (p=0.015). No difference at 11- months (p=0.12) or 5- years (p=0.11).</p>	NR
<p>Todd 2014³ 25129531</p>	NR	<p><u>Depression*</u> 6 months, ISS Depression Favors combination intervention ES=-0.44 (95% CI -0.83, -0.05)</p>	<p><u>Quality of Life*</u> 6 months, QoL.BD- Brief Favors combination intervention ES=0.42 (95% CI 0.04, 0.82)</p> <p><u>Social Function*</u> 6 months, SASS Favors combination intervention ES=0.54 (95% CI 0.14, 0.93)</p>	NR	NR

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Miklowitz 2003 ⁴ 12963672	<u>Relapse*</u> 12 months, Any Type NS OR=0.68 (95% CI 0.24, 1.85); p=0.50 <u>Time to Recurrence</u> 12 months Favors combination intervention HR=0.078, p<0.02 42.5 (2.2) weeks IFIT vs. 34.5 (2.5) weeks CM	<u>SADS-C Depression</u> 12 months Favors combination intervention, p < 0.0001. <u>SADS-C Mania</u> 12 months NS, p >0.10	NR	NR	NR

Abbreviations: AE=Adverse Events; BDI=Beck depression inventory; CI=Confidence Interval; CM=Clinical Management; ES=Effect Size; HR=Hazard Ratio; IFIT=Integrated Family and Individual Therapy; ISS=Internal States Scale; NR=not reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; QoL.BD-Brief=Quality of Life,Bipolar Disorder; SADS-C=Schedule for Affective Disorders and Schizophrenia-Change version; SASS=Simpson Angus Scale score; YMRS = Young Mania Rating Scale

Appendix Table O4. Summary of strength of evidence: combination intervention vs. inactive comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	12 months	1 Cohort Study (n=100)	No difference between groups at 12 months.	High	Unclear	Direct	Imprecise	Insufficient
Depression	7-12 months 5 years	3 RCTs (n=262)	Favors combination intervention across multiple time periods.	Low	Consistent	Direct	Imprecise	Insufficient
Mania	7-12 months 5 years	2 RCTs (n=140)	Mixed evidence with no clear direction of effect. No pattern across time periods.	Low	Unclear	Direct	Imprecise	Insufficient
Global Function	NR	-	-	-	-	-	-	-
Other Measures of Function	6 months	1 RCT (n=122)	Favors combination intervention at 6 months.	Moderate	Unclear	Direct	Imprecise	Insufficient

Abbreviations: NR=not reported; RCT=randomized controlled trial

Appendix Table O5. Characteristics of eligible studies: combination interventions vs. active comparators

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Fagiolini 2009 ⁵ RCT US Government Moderate 19500091	N=463 Age 41 (12-75) Female 61% White 83% BP I 68% BP II 19% BP NOS 11% Schizophrenia 2% Outpatient	No current clinical state excluded; BP I, II, or NOS or schizoaffective bipolar subtype disorder (DSM-IV for adults, KSADS-PL for adolescents). Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	Enhanced clinical intervention and specialized care for bipolar disorder. Enhanced clinical intervention consisted of 10 basic elements plus specific modules for young, elderly, and African American patients. Elements consisted of education (on disorder, medications, sleep) and management (review of symptoms, discussion and management of side effects, discussion of early waning signs). Additional non-specific support provided to both patient and families. -Weekly enhanced clinical sessions for 12 weeks, then every other week for 8 weeks, and then monthly for remaining time or until they achieved recurrence	Specialized care for bipolar disorder consisting of a manualized system of clinical management included assessment of quality of life, standardized assessments of mood, comprehensive medical evaluations, frequent visits with treatment team, pharmacological treatment and tracking and monitoring of visits.	18 months	CGI BP Depression CGI BP Mania GAF QLESQ Withdrawal 30%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Zaretsky 2008 ⁶ RCT Canada Government and Non- Government High 18674402	N=79 Age 41 (18-60) Female NR White NR BP I 66% BP II 34% Outpatient	Euthymic/Maintenance; BP I or II, not currently in a full episode, taking a standard mood stabilizer regimen with no change in regimen or prescribing physician in month prior to study entry. Substance Abuse; Schizoaffective; Other Mental Health; Neurological Disorders; Labs/Other Conditions	Psychoeducation and CBT. CBT was based on Basco and Rush manual and emphasized collaborative goal setting, cognitive restructuring, problem-solving, and enhancing interpersonal communication. -7 weekly, audiotaped individual sessions of psychoeducation and 13 weekly, audiotaped individual sessions of CBT	Psychoeducation based on the first five chapters of the Basco and Rush CBT manual. -7 weekly, audiotaped individual sessions	6 months	Relapse HDRS Withdrawal 42%

Abbreviations: BP=bipolar disorder; CBT=Cognitive Behavioral Therapy; CGI=Clinical Global Impressions Scale; DSM-IV= Diagnostic and statistical manual, 4th edition; GAF=General Assessment of Functioning Scale; HDRS=Hamilton Depression Rating Scale; KSADS-PL=Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial

Appendix Table O6. Summary risk of bias assessments: combination interventions vs. active comparators

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Fagiolini 2009 ⁵ Government 19500091	Moderate	Suspected selection bias due to unclear reporting of randomization process.
Zaretsky 2008 ⁶ Government and Non-Government 18674402	High	Suspected bias selection bias due to unclear reporting of randomization process and suspected bias due to attrition rate of 42%.

Abbreviations: PMID=PubMed Identification Number

Appendix Table O7. Outcomes Summary: combination interventions vs. active comparators

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Fagiolini 2009 ⁵ 19500091	NR	<u>Depression</u> 18 months, CGI Depression NS <u>Mania</u> 18 months, CGI Mania NS	<u>Global Function</u> 18 months, GAF NS <u>Quality of Life</u> 18 months, QLESQ Favors combination intervention.	NR	NR
Zaretsky 2008 ⁶ 18674402	<u>Relapse*</u> 12 months, Any Type NS OR=1.20 (95% CI 0.23, 6.80); p=0.55	<u>HDRS</u> 12 months Favors combination intervention, p=0.055	NR	NR	NR

Abbreviations: CGI=Clinical global impression scale; CI=Confidence Interval; GAF=General Assessment of Functioning Scale; HDRS=Hamilton Depression Rating Scale; NR=Not Reported; NS=not significant; OR=Odds Ratio; PMID=PubMed Identification Number; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire

Appendix Table O8. Summary of strength of evidence: combination intervention vs. active comparators

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	12 months	1 RCT (n=79)	No difference between groups at 12 months.	High	Unclear	Direct	Imprecise	Insufficient
Depression	12 months 18 months	2 RCTs (n=542)	Mixed evidence with no clear direction of effect. No pattern across time periods.	High	Inconsistent	Direct	Imprecise	Insufficient
Mania	18 months	1 RCT (n=463)	No difference between groups at 18 months.	High	Unclear	Direct	Imprecise	Insufficient
Global Function	18 months	1 RCT (n=463)	No difference between groups at 18 months	Moderate	Unclear	Direct	Imprecise	Insufficient
Other Measures of Function	18 months	1 RCT (n=463)	Favors combination intervention at 18 months.	Moderate	Unclear	Direct	Imprecise	Insufficient

Abbreviations: RCT=randomized controlled trial

References for Appendix O

1. Gonzalez Isasi A, Echeburua E, Liminana JM, et al. Psychoeducation and cognitive-behavioral therapy for patients with refractory bipolar disorder: A 5-year controlled clinical trial. *European Psychiatry*. Dec. 2014 March 2014(Pagination)PMID 23276524.
2. Gonzalez-Isasi A, Echeburua E, Mosquera F, et al. Long-term efficacy of a psychological intervention program for patients with refractory bipolar disorder: a pilot study. *Psychiatry Research*. 2010 Apr 30;176(2-3):161-5. PMID 20096466.
3. Todd NJ, Jones SH, Hart A, et al. A web-based self-management intervention for Bipolar Disorder 'living with bipolar': a feasibility randomised controlled trial. *J Affect Disord*. 2014 Dec;169:21-9. PMID 25129531.
4. Miklowitz DJ, George EL, Richards JA, et al. A randomized study of family-focused psychoeducation and pharmacotherapy in the outpatient management of bipolar disorder. *Archives of General Psychiatry*. 2003 Sep;60(9):904-12. PMID 12963672.
5. Fagiolini A, Frank E, Axelson DA, et al. Enhancing outcomes in patients with bipolar disorder: results from the Bipolar Disorder Center for Pennsylvanians Study. *Bipolar Disorders*. 2009 Jun;11(4):382-90. PMID 19500091.
6. Zaretsky A, Lancee W, Miller C, et al. Is cognitive-behavioural therapy more effective than psychoeducation in bipolar disorder? *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*. 2008 Jul;53(7):441-8. PMID 18674402.

Appendix P. Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Study and Other Psychosocial and Somatic Interventions

Appendix Table P1. Characteristics of eligible studies: STEP-BD study and other psychosocial interventions

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Depp, 2015 ¹ RCT US Government Low 25479050	N=104 Age 48 (22-74) Female 59% White 70% BP I 88% BP II 12% Outpatient	Without severe symptoms; Outpatients with BP (DSM-IV) currently prescribed medications for bipolar disorder without severe depressive (MADRS >32) or manic (YMRS> 20) Substance Abuse; Other Mental Health	Psychoeducation followed by use of a smart phone that delivered interactive elements via a mobile web-based program that delivered questionnaires and responses based on symptoms or early warning signs -4 sessions of psychoeducation followed by smart intervention (2 surveys per day) for 10 weeks	Psychoeducation followed by binder with paper and pencil mood charts. Monitored remotely via cell phone and had to turn in completed charts at the end of study. -4 sessions of psychoeducation followed by mood charts once per day for 10 weeks	6 months	MADRS YMRS Withdrawal 22%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Faurholt-Jepsen, 2015 ² RCT Denmark Government and Non-Government Low 26220802	N=78 Age 29 (18-60) Female 82% White NR BP I 82% Outpatient	No current clinical state excluded; Individuals with a BP diagnosis (ICD-10 and Schedules for Clinical Assessment in Neuropsychiatry) with a HDRS ≤ 17 and a YMRS ≤ 17 Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	Smartphone with self-monitoring system that documented mood, sleep length, activity, medication taken, irritability, cognitive problems, alcohol consumption, stress, menstruation, and early warning signs. Patients could see visual representations of data to self-monitor. System included feedback loop with clinic and contact with study nurse. -6 months of self-monitoring	Smartphone without self-monitoring system and nurse contact if needed. -6 months of smart phone access	6 months	HAMD-17 YMRS FAST WHO-Qol-bref Withdrawal 14%

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Followup Duration	Outcomes Reported Withdrawal (%) at endpoint
Deckersbach 2014 ³ Miklowitz 2007 ⁴ Miklowitz 2007b ⁵ RCT US Government and Non-Government High Moderate High 24077657 17728418 17404119	N=293 Age 40 (18-62) Female 59% White 91% BP I 67% BP II 31% BP NOS 2% Outpatient	Major Depressive Episode; BP I or II (DSM-IV) with current major depressive episode (but no mixed episode or depression not otherwise specified), currently being treated with a mood stabilizer (or willing to initiate), not currently undergoing psychotherapy (or willing to discontinue) Substance Abuse; Other Mental Health; Pregnant/Nursing; Labs/Other Conditions	Intensive psychotherapy consisting of one of the following: 1) individual CBT consisting psychoeducation, life events scheduling, cognitive restructuring, problem-solving, strategies for early detection, and interventions for comorbidities, 2) IPSRT consisting of selecting a primary problem area and teaching patients about the Social Rhythm Metric and interpersonal problem resolution, or 3) family- focused therapy which encouraged patients and relatives to develop a common understanding, develop a relapse prevention plan, participate in communication enhancement exercises, and identify and solve problems related to illness or the home environment. -30 50-minute sessions over 9 months	Collaborative care consisting of a reviewing a psychoeducational videotape and workbook and developing a treatment contract. Workbook included information about BP, schedule management and mood charting, improving communication skills, an developing a treatment contract. -Three 50-minute individual sessions	12 months	Recovery LIFE-RIFT Withdrawal 48%

Abbreviations: BP=bipolar disorder; CBT= Cognitive Behavioral Therapy; DSM=Diagnostic and Statistical Manual of Mental Disorders; FAST= Functioning Assessment Short Test; HAMD-17= Hamilton Rating Scale for Depression (17-items); HDRS= Hamilton Depression Rating Scale; ICD-10= International Statistical Classification of Diseases and Related Health Problems- 10th Revision; IPSRT=Interpersonal and Social Rhythm Therapy; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; WHO-QOL-bref= World Health Organization Quality of Life-short version; YMRS = Young Mania Rating Scale

Appendix Table P2. Summary risk of bias assessments: STEP-BD study and other psychosocial interventions

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Depp, 2015 ¹ Government 25479050	Low	No significant suspected biases.
Faurholt-Jepsen, 2015 ² Government and Non-Government 26220802	Low	No significant suspected biases.
Deckersbach 2014 ³ Miklowitz 2007 ⁴ Miklowitz 2007b ⁵ Government and Non-Government 24077657 17728418 17404119	High Moderate High	Suspected bias due to attrition rate of 48%. Part of analysis only includes subset of subjects from total study population.

Abbreviations: PMID=PubMed Identification Number

Appendix Table P3. Outcomes summary: STEP-BD Study and other psychosocial interventions

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Depp, 2015 ¹ 25479050	NR	<u>Depression</u> 6 months, MADRS NS ES=0.02; p=0.05 <u>Mania</u> 6 months, YMRS NS ES=-0.09;p=0.26	NR	NR	NR
Faurholt-Jepsen, 2015 ² 26220802	NR	<u>Depression</u> 6 months, HAMD-17 NS Adjusted Difference: 0.96 (95% CI -4.36, 6.28); p=0.72 <u>Mania</u> 6 months, YMRS NS Adjusted Difference= -0.34 (95% CI -1.14, 0.47); p=0.41	<u>Global Function</u> 6 months, FAST NS Adjusted Difference= 0.96 (95% CI -4.36, 6.28); p=0.72 <u>Quality of Life</u> NS 6 months, WHO-QOL-bref Adjusted Difference= 1.24 (95% CI -5.18, 2.70); p=0.54	NR	NR
Deckersbach 2014 ³ 24077657 Miklowitz 2007 ⁴ 17728418 Miklowitz 2007b ⁵ 17404119	<u>Number Recovered</u> 1 year Favors intensive psychosocial intervention HR 1.47; p= .01 Family Therapy: HR 1.87 IPSRT: HR 1.48 CBT: HR 1.34	NR	<u>Functional Impairment</u> 9 months, LIFT-RIFT Favors intensive psychosocial intervention, p=0.04 Mean Difference (SD) Family Therapy: -3.17 (3.06) IPSRT: -1.63 (4.35) CBT: -1.05 (4.77) Collaborative Care: -0.94 (3.5)	NR	NR

Abbreviations: AE=Adverse Events; CBT= Cognitive Behavioral Therapy; CI=Confidence Interval; ES=Effect Size; FAST= Functioning Assessment Short Test; HAMD-17= Hamilton Rating Scale for Depression (17-items); HR=Hazard Ratio; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; IPSRT= Interpersonal and Social Rhythm Therapy; NR=not reported; NS=not significant; PMID=PubMed Identification Number; SD=standard deviation; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table P4. Summary of strength of evidence: other psychosocial interventions, self-management interventions

Outcome	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Relapse	NR	-	-	-	-	-	-	-
Depression	6 months	2 RCTs (n=182)	No difference between groups in MADRS at 6 months.	Low	Consistent	Direct	Imprecise	Insufficient
Mania	6 months	2 RCTs (n=182)	No difference between groups in YMRS at 6 months.	Low	Consistent	Direct	Imprecise	Insufficient
Global Function	6 months	1 RCT (n=78)	No difference between groups at 6 months. FAST Adjusted Difference= 0.96 (95% CI -4.36, 6.28); p=0.72	Low	Unclear	Direct	Imprecise	Insufficient
Other Measures of Function	6 months	1 RCT (n=78)	No difference between groups at 6 months. WHO-QOL-bref Adjusted Difference= 1.24 (95% CI -5.18, 2.70); p=0.54	Low	Unclear	Direct	Imprecise	Insufficient

Abbreviations: CI=Confidence Interval; FAST= Functioning Assessment Short Test; MADRS=Montgomery-Asberg Depression Rating Scale; NR=not reported; RCT=randomized controlled trial; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table P5. Characteristics of eligible studies: somatic therapy

Study, Year Design Location Funder Risk of Bias PMID	Randomized (N) Age (mean) Sex (% Female) Race (% White) Diagnosis (% BP I, II, NOS) Setting	Inclusions Key Exclusions	Intervention Description	Comparison Description	Follow-up Duration	Outcomes Reported Withdrawal (%) at endpoint
Fitzgerald, 2016 ⁶ RCT Australia Government Medium 27016659	N = 46 Age 46 (33-59) Female 57% Race NR BP I 63% BP II 37% Outpatient	Depression; Individuals with BP I or II (DSM-IV) with persistent depressive symptoms (HAM-D > 20) who failed to respond to at least two courses of anti-depressants for at least 6 weeks in current episode. No increase or initiation of new treatment in the four weeks prior to rTMS. Labs/Other Conditions; Neurological Disorder	Repetitive transcranial magnetic stimulation -20 rTMS sessions for four weeks	Sham stimulation -20 sham sessions for four weeks	4 weeks	HAM-D Response Remission (Not Defined) Withdrawal 13%

Abbreviations: BP=bipolar disorder; CBT= Cognitive Behavioral Therapy; DSM=Diagnostic and Statistical Manual of Mental Disorders; FAST= Functioning Assessment Short Test; HAMD-17= Hamilton Rating Scale for Depression (17-items); HDRS= Hamilton Depression Rating Scale; ICD-10= International Statistical Classification of Diseases and Related Health Problems- 10th Revision; IPSRT=Interpersonal and Social Rhythm Therapy; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool; MADRS=Montgomery-Asberg Depression Rating Scale; NOS=not otherwise specified; NR=not reported; PMID=PubMed Identification Number; RCT=randomized controlled trial; WHO-QOL-bref= World Health Organization Quality of Life–short version; YMRS = Young Mania Rating Scale

Appendix Table P6. Summary risk of bias assessments: somatic therapy

Study Funder PMID	Overall Risk of Bias Assessment	Rationale
Fitzgerald, 2016 ⁶ Government 27016659	Moderate	Suspected bias due to unclear reporting of attrition/loss to followup.

Abbreviations: PMID=PubMed Identification Number

Appendix Table P7. Outcomes summary: somatic therapy

Study PMID	Responder/Remitter	Symptom	Function	Other	AE
Fitzgerald, 2016 ⁶ 27016659	<u>Response</u> 4 weeks NS; p<0.05 rTMS=3 Sham=1 <u>Remission</u> 4 weeks NS; p<0.05 rTMS=2 Sham=0	<u>Depression*</u> 4 weeks, HAM-D NS ES=-0.04 (95% CI -0.62, 0.54)	NR	NR	NR

Abbreviations: AE=Adverse Events; CI=Confidence Interval; ES=Effect Size;

References for Appendix P

1. Depp CA, Ceglowski J, Wang VC, et al. Augmenting psychoeducation with a mobile intervention for bipolar disorder: a randomized controlled trial. *Journal of Affective Disorders*. 2015 Mar 15;174:23-30. doi: <http://dx.doi.org/10.1016/j.jad.2014.10.053>. PMID: 25479050.
2. Faurholt-Jepsen M, Frost M, Ritz C, et al. Daily electronic self-monitoring in bipolar disorder using smartphones - the MONARCA I trial: a randomized, placebo-controlled, single-blind, parallel group trial. *Psychological Medicine*. 2015 Oct;45(13):2691-704. doi: <http://dx.doi.org/10.1017/S0033291715000410>. PMID: 26220802.
3. Deckersbach T, Peters AT, Sylvia L, et al. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *American Journal of Psychiatry*. 2014 Feb;171(2):178-86. doi: <http://dx.doi.org/10.1176/appi.ajp.2013.13020225>. PMID: 24077657.
4. Miklowitz DJ, Otto MW, Frank E, et al. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. *American Journal of Psychiatry*. 2007 Sep;164(9):1340-7. PMID: 17728418.
5. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Archives of General Psychiatry*. 2007 Apr;64(4):419-26. PMID: 17404119.
6. Fitzgerald PB, Hoy KE, Elliot D, et al. A negative double-blind controlled trial of sequential bilateral rTMS in the treatment of bipolar depression. *Journal of Affective Disorders*. 2016 01 Jul;198:158-62. doi: <http://dx.doi.org/10.1016/j.jad.2016.03.052>. PMID: 27016659 PMID/609157504 Embase.

Appendix Q. Harms Tables

Appendix Table Q1. FDA box warnings for drugs used for bipolar treatment

Drug	Box Warning
Aripiprazole	Increased mortality in elderly patients with dementia related psychosis. IRisk of suicide among adolescents.
Asenapine	Increased mortality In elderly patients with dementia related psychosis.
Carbamazepine	<p>Risk of suicide.</p> <p>Serious, sometimes fatal dermatologic reactions reported, including toxic epidermal necrolysis and Stevens-Johnson syndrome. Risk 10x greater in some Asian countries; strong associated between risk and HLA-B*1502 allele, which is found almost exclusively in Asian patients.</p> <p>Transient or persistent decreased platelet or white blood cell counts not uncommon with carbamazepine but majority of leukopenia cases do not progress to aplastic anemia or agranulocytosis. Perform baseline and periodic hematological testing. Consider discontinuing treatment if evidence of significant bone marrow depression.</p>
Cariprazine	Increased mortality In elderly patients with dementia related psychosis.
Lamotrigine	<p>Risk of suicide.</p> <p>Serious skin rashes.</p>
Lithium	Lithium toxicity can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.
Olanzapine	Increased mortality In elderly patients with dementia related psychosis. When used in combination with fluoxetine also warn against suicidality and antidepressant drugs.
Quetiapine	Increased mortality in elderly patients with dementia related psychosis. Risk of suicide among adolescents.
Risperidone	Increased mortality In elderly patients with dementia related psychosis.

Drug	Box Warning
Valproic acid/ valproate/ divalproex (same for all)	<p>Risk of suicide.</p> <p>Serious or fatal hepatotoxicity has occurred, usually during first six months of treatment. Patients <2 years old are at increased risk, especially with the following comorbidities: multiple anticonvulsant treatment, congenital metabolic disorder, severe seizure disorder with mental retardation, or organic brain disorders.</p> <p>Increased risk of acute liver failure and death in patients with hereditary neurometabolic syndromes caused by mitochondrial DNA polymerase gamma gene mutations (e.g. Alpers Huttenlocher Syndrome).</p> <p>Fetal risk via major congenital malformations including neural tube defects and decreased IQ scores after in utero exposure.</p> <p>Life threatening pancreatitis including hemorrhagic cases with rapid progression from initial symptoms to death reported in children and adults.</p>
Ziprasidone	Increased mortality In elderly patients with dementia related psychosis.
Allopurinol	None
Bupropion	<p>Risk of suicide among adolescents.</p> <p>Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation.</p>
Celecoxib	<p>May cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.</p> <p>Increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, particularly in elderly patients.</p>
Citalopram	Risk of suicide among adolescents.
Dipyridamole	None
Donepezil	None
Fluoxetine	Risk of suicide among adolescents.
Gabapentin	Risk of suicide.
Haloperidol	Increased mortality In elderly patients with dementia related psychosis.
Memantine	None
Oxcarbazepine	Risk of suicide.
Paliperidone	Increased mortality In elderly patients with dementia related psychosis.
Paroxetine	Risk of suicide among adolescents.
Perphenazine	Increased mortality In elderly patients with dementia related psychosis.
Ramelteon	None

Drug	Box Warning
Tamoxifen	Women with ductal carcinoma in situ and at high risk for breast cancer at increased risk of uterine malignancies, stroke and pulmonary embolism.
Topiramate	Risk of suicide.
Venlafaxine	Risk of suicide among adolescents.
Verapamil	None

Sources:

www.fda.gov/

www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders

Abbreviations: FDA=United States Food and Drug Administration

Appendix Table Q2. Previously reported side effects* of bipolar medications

Drug Generic Name (Trade Names)	Side Effects
Aripiprazole (Abilify) ¹	<ul style="list-style-type: none"> Cardiovascular: Cardiorespiratory arrest (0.1% to 1%), Cardiorespiratory failure (0.1% to 1%), Myocardial infarction (0.1% to 1%), Prolonged QT interval (0.1% to 1%) Endocrine metabolic: Diabetic ketoacidosis (Less than 0.1%) Gastrointestinal: Pancreatitis Hematologic: Agranulocytosis, Leukopenia (Less than 1%), Neutropenia (Less than 1%) Musculoskeletal: Rhabdomyolysis (Less than 0.1%) Neurologic: Cerebrovascular accident, Seizure (Up to 0.3%), Tardive dyskinesia, Transient ischemic attack Psychiatric: At risk for suicide, Suicidal behavior Other: Angioedema (0.1% to less than 1%), Increased body temperature, Neuroleptic malignant syndrome Neurologic: Akathisia (2% to 25%), Dizziness (4% to 10%), Extrapyrimal sign (2% to 27.3%), Headache (10% to 27%), Insomnia (8% to 18%), Sedated (3% to 21%), Somnolence (6% to 26.3%), Tremor (2% to 11.8%)
Asenapine (Saphris) ¹	<ul style="list-style-type: none"> Cardiovascular: Prolonged QT interval Endocrine metabolic: Hyperglycemia (Adult, 1.7% to 15.8%; pediatric up to 1.8%), Serum cholesterol abnormal (Adult, 0% to 14.7%; pediatric, 0% to 9.6%), Serum triglycerides raised, Or altered (Adult, 1.6% to 8.3%; pediatric, 1.9% to 4%), Weight increased (Adult, 1% to 22%; pediatric, 2% to 12%) Hematologic: Agranulocytosis, Decreased blood leukocyte number, Neutropenia Immunologic: Hypersensitivity reaction Neurologic: Somnolence (Adult, 13% to 26%; pediatric, 46% to 53%) Psychiatric: Suicidal thoughts (1% to 4%) Other: Angioedema, Death, Neuroleptic malignant syndrome Neurologic: Akathisia (Adult, 4% to 15%; pediatric, 1% to 2%), Dizziness (Adult, 3% to 8%; pediatric, 5% to 10%), Extrapyrimal disease (6% to 12%)

Drug Generic Name (Trade Names)	Side Effects
Carbamazepine (Carbetrol, Epitol, Equetro, Tegretol, Teril) ¹	<ul style="list-style-type: none"> Cardiovascular: Atrioventricular block, Cardiac dysrhythmia, Congestive heart failure, Eosinophilic myocarditis, Hypersensitivity, Syncope Dermatologic: Stevens-Johnson syndrome, Toxic epidermal necrolysis Endocrine metabolic: Hypocalcemia, Hyponatremia (Oral, 4% to 21.7%; IV, less than 2%), Water intoxication syndrome Gastrointestinal: Pancreatitis Hematologic: Agranulocytosis, Aplastic anemia, Bone marrow depression, Eosinophil count raised, Leukopenia, Pancytopenia, Thrombocytopenia Hepatic: Hepatitis, Liver damage, Liver failure, Vanishing bile duct syndrome Immunologic: Drug reaction with eosinophilia and systemic symptoms Neurologic: Acute intermittent porphyria Renal: Azotemia, Renal failure Respiratory: Pulmonary hypersensitivity Other: Angioedema Neurologic: Asthenia (8%), Ataxia (15%), Dizziness (Bipolar disorder, 44%; seizures, 9%), Somnolence (Bipolar disorder, 32%; seizures, 5%)
Cariprazine (Vraylar) ¹	<ul style="list-style-type: none"> Cardiovascular: Ischemic stroke (Up to 0.1%), Orthostatic hypotension Endocrine metabolic: Diabetes mellitus, Dyslipidemia, Hyperglycemia Gastrointestinal: Esophageal dysmotility Hematologic: Leukopenia, Neutropenia Musculoskeletal: Tardive dyskinesia Neurologic: Seizure Psychiatric: At risk for suicide (Up to 1%), Loss of judgement Respiratory: Pulmonary aspiration Other: Body temperature finding, Body temperature dysregulation, Neuroleptic malignant syndrome Neurologic: Akathisia (Schizophrenia, 9%; bipolar, 20%), Extrapyrasidal sign (Schizophrenia, 15%; bipolar, 26%), Somnolence (5% to 8%)
Lamotrigine (Lamictal) ¹	<ul style="list-style-type: none"> Dermatologic: Erythema multiforme (less than 0.1%), Rash, Serious (0.08% to 0.8%), Stevens-Johnson syndrome, Toxic epidermal necrolysis Hematologic: Anemia (immediate release, less than 0.1%), Disseminated intravascular coagulation, Eosinophil count raised (immediate release, less than 0.1%), Leukopenia (immediate release, 0.1% to 1%), Thrombocytopenia (immediate release, less than 0.1%) Hepatic: Liver failure Immunologic: Drug reaction with eosinophilia and systemic symptoms Neurologic: Aseptic meningitis Other: Angioedema (less than 0.1%), Neuroleptic malignant syndrome Neurologic: Asthenia (immediate-release, 2% to 8%; extended-release, 6%), Ataxia (immediate-release, 2% to 11%), Coordination problem (immediate-release, 6% to 7%; extended-release, 3%), Dizziness (immediate-release, 7% to 54%; extended release, 14%), Headache (immediate-release, 29%), Insomnia (immediate-release, 5% to 10%), Somnolence (immediate-release, 9% to 17%; extended-release, 5%), Tremor (immediate-release, 4% to 10%; extended-release, 6%), Vertigo (immediate-release, 2%; extended-release, 3%)

Drug Generic Name (Trade Names)	Side Effects
Lithium ³	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch • Black Box Warning: Lithium toxicity can occur at doses close to therapeutic levels. Keep all appointments to check response to lithium. • unusual tiredness or weakness • excessive thirst • frequent urination • slow, jerky movements • movements that are unusual or difficult to control • blackouts • seizures • fainting • dizziness or lightheadedness • fast, slow, irregular, or pounding heartbeat • shortness of breath • chest tightness • confusion • hallucinations (seeing things or hearing voices that do not exist) • crossed eyes • painful, cold, or discolored fingers and toes • headache • pounding noises inside the head • swelling of the feet, ankles, or lower legs
Olanzapine (Zyprexa) ¹	<ul style="list-style-type: none"> • Cardiovascular: Sudden cardiac death • Endocrine/metabolic: Diabetes mellitus, Diabetic coma with ketoacidosis, Diabetic ketoacidosis, Hyperglycemic hyperosmolar state • Gastrointestinal: Acute hemorrhagic pancreatitis • Hematologic: Leukopenia, Venous thromboembolism • Immunologic: Drug reaction with eosinophilia and systemic symptoms, Hypersensitivity reaction • Neurologic: Cerebrovascular disease, Dystonia (2% to 3%), Seizure (0.9%), Status epilepticus • Psychiatric: Suicidal intent (0.1% to 1%) • Respiratory: Pulmonary embolism • Neurologic: Akathisia (5% to 27%), Asthenia (2% to 20%), Dizziness (Adult, 1.6% to 18%; adolescent, 7% to 8%), Somnolence (IM, 6%; oral, 20% to 52%), Tremor (1% to 23%)
Quetiapine ² (Seroquel)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Changes in mood or behavior, agitation, anxiety, restlessness, or thoughts of hurting yourself or others • Constant muscle movement that you cannot control (often in your lips, tongue, jaw, arms, or legs) • Fast, slow, pounding, or uneven heartbeat • Fever, chills, cough, sore throat, and body aches • Fever, sweating, confusion, uneven heartbeat, muscle stiffness • Increase in how much or how often you urinate, increased thirst, increased hunger, or weakness • Lightheadedness, dizziness, fainting, or clumsiness • Seizures • Vision changes

Drug Generic Name (Trade Names)	Side Effects
Risperidone (Risperdal) ¹	<ul style="list-style-type: none"> Cardiovascular: Prolonged QT interval, Sudden cardiac death, Syncope (oral, up to 1%; IM, up to 2%) Endocrine metabolic: Diabetic ketoacidosis, Hypothermia Gastrointestinal: Pancreatitis Hematologic: Agranulocytosis, Leukopenia, Neutropenia, Thrombocytopenia, Thrombotic thrombocytopenic purpura Neurologic: Cerebrovascular accident, Seizure (0.3%), Tardive dyskinesia (oral, less than 5%; IM, less than 4%) Reproductive: Priapism Respiratory: Pulmonary embolism Other: Neuroleptic malignant syndrome Neurologic: Akathisia (oral, up to 10%; IM, 4% to 11%), Dizziness (oral, 4% to 16%; IM, 3% to 11%), Dystonia (oral, adult, 3% to 5%; pediatric, 2% to 6%; IM, adult, less than 4%), Parkinsonism (oral, 6% to 28%; IM, 8% to 15%), Sedated (5% to 63%), Tremor (oral, 2% to 12%; IM, 3% to 24%)
Valproic acid (Depakene, Stavzor, Valproic) ¹	<ul style="list-style-type: none"> Cardiovascular: Palpitations (1% to less than 5%), Tachycardia (1% to less than 5%) Endocrine metabolic: Hyperammonemia Gastrointestinal: Hematemesis (1% to less than 5%) Hematologic: Myelodysplastic syndrome, Thrombocytopenia, Dose-related (1% to 27%) Immunologic: Hypersensitivity reaction (rare) Neurologic: Coma, Hyperammonemia-induced, Encephalopathy, Hyperammonemic encephalopathy Otic: Ototoxicity - deafness (1% to less than 5%) Respiratory: Pleural effusion (rare) Neurologic: Amnesia (4% to 7%), Asthenia (10% to 27%), Ataxia (8%), Dizziness (12% to 25%), Headache (5% to 31%), Insomnia (9% to 15%), Somnolence (17% to 30%), Tremor (9% to 57%) Neurologic: Amnesia (4% to 7%), Asthenia (10% to 27%), Ataxia (8%), Dizziness (12% to 25%), Headache (5% to 31%), Insomnia (9% to 15%), Somnolence (17% to 30%), Tremor (9% to 57%)
Divalproex (Depakote) ¹	<ul style="list-style-type: none"> Cardiovascular: Palpitations (greater than 1% to less than 5%), Tachycardia (greater than 1% to less than 5%) Endocrine metabolic: Hyperammonemia Gastrointestinal: Pancreatitis (greater than 1% to less than 5%) Hematologic: Myelodysplastic syndrome, Thrombocytopenia, Dose-related (1% to 27%) Hepatic: Liver failure Immunologic: Drug reaction with eosinophilia and systemic symptoms (rare) Neurologic: Hyperammonemic encephalopathy Otic: Ototoxicity - deafness (greater than 1% to less than 5%) Neurologic: Asthenia (6% to 27%), Dizziness (up to 25%), Feeling nervous (up to 11%), Headache (31%), Insomnia (up to 15%), Somnolence (Adult, 7% to 30%; pediatric, greater than 5%), Tremor (1% to 57%)
Valproate (Depacon) ¹	<ul style="list-style-type: none"> Endocrine metabolic: Hyperammonemia Gastrointestinal: Pancreatitis Hematologic: Myelodysplastic syndrome, Thrombocytopenia (27%) Hepatic: Liver failure Immunologic: Drug reaction with eosinophilia and systemic symptoms Neurologic: Hyperammonemic encephalopathy

Drug Generic Name (Trade Names)	Side Effects
Ziprasidone ³ (Geodon)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DolntegratedSearch# • unusual movements of your face or body that you cannot control • fast, irregular, or pounding heartbeat • rash or hives • itching • blisters or peeling of skin • mouth sores • swollen glands • fever or chills • shaking • muscle stiffness • confusion • sweating • loss of consciousness • painful erection of the penis that lasts for hours
Allopurinol ¹ (Aloprim, Zyloprim)	<ul style="list-style-type: none"> • Dermatologic: Drug reaction with eosinophilia and systemic symptoms, Rash (up to 3%), Stevens-Johnson syndrome (less than 1%), Toxic epidermal necrolysis (less than 1%) • Hematologic: Agranulocytosis, Aplastic anemia, Eosinophil count raised, Myelosuppression, Thrombocytopenia (0.6%) • Hepatic: Granulomatous hepatitis (less than 1%), Hepatic necrosis (less than 1%), Hepatotoxicity • Immunologic: Hypersensitivity reaction • Renal: Renal failure (less than 1%)
Bupropion ² (Aplenzin, Wellbutrin, Zyban)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DolntegratedSearch# • Blistering, peeling, or red skin rash • Chest pain, trouble breathing, fast, slow, or uneven heartbeat • Muscle or joint pain, fever with rash • Seeing or hearing things that are not there, feeling like people are against you • Seizures or tremors • Sudden increase in energy, racing thoughts, trouble sleeping • Thoughts of hurting yourself, worsening depression, severe agitation or confusion
Celecoxib (Celebrex) ¹	<ul style="list-style-type: none"> • Cardiovascular: Myocardial infarction (Osteoarthritis or rheumatoid arthritis, 0.1% to 1.9%), Torsades de pointes, Ventricular hypertrophy (familial adenomatous polyposis, 0.1% to 1%) • Dermatologic: Erythema multiforme, Erythroderma, Generalized exanthematous pustulosis, acute, Stevens-Johnson syndrome, Toxic epidermal necrolysis • Endocrine metabolic: Hyperkalemia • Gastrointestinal: Gastrointestinal hemorrhage (Osteoarthritis or rheumatoid arthritis, less than 0.1%), Gastrointestinal perforation (Osteoarthritis or rheumatoid arthritis, less than 0.1%), Gastrointestinal ulcer, Inflammatory disorder of digestive tract • Hematologic: Hemorrhage, Thrombosis (familial adenomatous polyposis, 1.2%) • Hepatic: Fulminant hepatitis, Hepatotoxicity (Rare), Increased liver enzymes (Osteoarthritis or rheumatoid arthritis, 0.1% to 1.9%), Liver failure • Immunologic: Anaphylactoid reaction, Drug reaction with eosinophilia and systemic symptoms • Neurologic: Cerebrovascular accident • Renal: Acute renal failure, Injury of kidney • Respiratory: Asthma, Bronchospasm (arthritis, 0.1% to 1.9%)

Drug Generic Name (Trade Names)	Side Effects
Citalopram ² (Celexa)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there • Chest pain, trouble breathing • Confusion, weakness, and muscle twitching • Fast, pounding, or uneven heartbeat • Feeling more excited or energetic than usual, trouble sleeping, racing thoughts • Eye pain, vision changes, seeing halos around lights • Lightheadedness, dizziness, fainting • Painful, prolonged erection of your penis • Thoughts of hurting yourself or others, unusual behavior • Unusual bleeding or bruising
Dipyridamole (Persantine) ¹	<ul style="list-style-type: none"> • Cardiovascular: Angina pectoris, Cardiac arrest, Myocardial infarction (IV, 0.1%), Myocardial ischemia, Ventricular fibrillation, Ventricular tachycardia (IV, 0.2%) • Hepatic: Liver failure • Immunologic: Hypersensitivity reaction • Neurologic: Cerebrovascular accident, Seizure • Respiratory: Bronchospasm (IV, 0.2%)
Donepezil ² (Aricept)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing • Bloody or black, tarry stools • Change in how much or how often you urinate • Chest pain, slow or uneven heartbeat, trouble breathing • Lightheadedness, dizziness, fainting • Seizures • Severe stomach pain • Unusual bleeding, bruising, or weakness • Vomiting of blood or material that looks like coffee grounds
Fluoxetine ² (Prozac, Sarafem)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there • Confusion, weakness, and muscle twitching • Eye pain, trouble seeing, blurry vision • Fast, pounding, or uneven heartbeat, dizziness • Seizures • Skin rash, blisters, peeling, or redness • Trouble breathing • Unusual behavior, thoughts of hurting yourself or others, feeling more excited or energetic than usual, trouble sleeping • Unusual bleeding or bruising

Drug Generic Name (Trade Names)	Side Effects
Gabapentin (Gralise, Horizant, Neurontin) ¹	<ul style="list-style-type: none"> • Dermatologic: Stevens-Johnson syndrome • Endocrine metabolic: Hypoglycemia • Immunologic: Anaphylaxis, Drug reaction with eosinophilia and systemic symptoms • Neurologic: Dizziness (Adults, 28%; adults and adolescents, 17%; pediatrics, 3%), Somnolence (Adults, 21%; adults and adolescents, 19%; pediatrics, 8%) • Psychiatric: Disorder of form of thought (Pediatric, 1.7%), Disturbance in thinking (2% to 3%), Hostile behavior (Pediatric, 5.2%), Hyperactive behavior (Pediatric, 4.7%), Mood swings (Pediatric, 6%), Suicidal thoughts • Other: Angioedema • Neurologic: Ataxia (Adult, 3%; adult and adolescent, 13%), Nystagmus (Adult and adolescent, 8%)
Haloperidol (Haldol) ¹	<ul style="list-style-type: none"> • Cardiovascular: Prolonged QT interval, Sudden cardiac death, Torsades de pointes • Gastrointestinal: Paralytic ileus • Hematologic: Agranulocytosis • Neurologic: Dystonia, Neuroleptic malignant syndrome, Seizure, Tardive dyskinesia • Reproductive: Priapism • Neurologic: Akathisia, Extrapyramidal disease (Frequent), Somnolence
Memantine ² (Namenda)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evindencexpert.DoIntegratedSearch# • Change in how much or how often you urinate. • Chest pain. • Lightheadedness, dizziness, or fainting. • Seeing or hearing things that are not there. • Severe sleepiness, restlessness, or confusion. • Sudden or severe headache.
Oxcarbazepine (Trileptal) ¹	<ul style="list-style-type: none"> • Dermatologic: Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis • Endocrine metabolic: Hyponatremia (1% to 5%) • Hematologic: Agranulocytosis, Leukopenia, Pancytopenia • Immunologic: Anaphylaxis, Hypersensitivity reaction, Multiorgan • Neurologic: Status epilepticus • Psychiatric: Suicidal thoughts • Other: Angioedema • Neurologic: Abnormal gait (Up to 17%), Ataxia (Adult, 1% to 31%; pediatric, 13%), Dizziness (Adult, 8% to 49%; pediatric, 28%), Headache (Adult, 8% to 32%; pediatric, 31%), Impairment of balance (5% to 7%), Somnolence (Adult, 5% to 36%; pediatric, 31% to 34.8%), Tremor (1% to 16%)
Paliperidone (Invega) ¹	<ul style="list-style-type: none"> • Cardiovascular: Prolonged QT interval (7%) • Hematologic: Agranulocytosis, Leukopenia • Neurologic: Dysphagia, Tardive dyskinesia • Reproductive: Priapism • Neurologic: Akathisia (3% to 17%), Dyskinesia (1% to 6%), Dystonia (1% to 14%), Extrapyramidal disease (4% to 23%), Parkinsonism (Up to 14%), Somnolence (6% to 26%), Tremor (2% to 12%)

Drug Generic Name (Trade Names)	Side Effects
Paroxetine ² (Brisdelle, Paxil, Pexeva)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evindencexpert.DolntegratedSearch# • Anxiety, restlessness, fast heartbeat, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there • Bone pain, tenderness, swelling, or bruising • Changes in behavior, thoughts of hurting yourself or others • Confusion, weakness, and muscle twitching • Eye pain, vision changes, seeing halos around lights • Trouble keeping still, feeling restless and agitated, racing thoughts, excessive energy, trouble sleeping • Unusual bleeding or bruising
Perphenazine (Trilafon) ¹	<ul style="list-style-type: none"> • Cardiovascular: Prolonged QT interval, Torsades de pointes • Gastrointestinal: Obstipation (rare), Paralytic ileus (rare) • Hematologic: Agranulocytosis (rare), Disorder of hematopoietic structure (rare), Leukopenia (rare), Thrombocytopenia (rare) • Immunologic: Drug-induced lupus erythematosus, Systemic (rare) • Neurologic: Ineffective thermoregulation, Heatstroke or hypothermia (rare), Neuroleptic malignant syndrome (rare), Seizure (rare) • Reproductive: Priapism (rare) • Other: Death • Neurologic: Akathisia, Dizziness, Drug-induced tardive dystonia, Dystonia, Extrapyrimal disease, Parkinsonian, Somnolence, Tardive dyskinesia
Ramelteon (Rozerem) ¹	<ul style="list-style-type: none"> • Psychiatric: Depression, worsening, Hallucinations, Mania • Other: Angioedema (rare)
Tamoxifen ² (Nolvadex, Soltamox)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evindencexpert.DolntegratedSearch# • Chest pain, shortness of breath, or coughing up blood. • Dark-colored urine or pale stools. • Fever, chills, cough, sore throat, and body aches. • Heavy or abnormal vaginal bleeding, pelvic pain or pressure. • Nausea, vomiting, loss of appetite, or pain in your upper stomach. • New breast lumps. • Numbness or weakness in your arm or leg, or on one side of your body. • Pain in your lower leg (calf). • Sudden or severe headache, or problems with vision, speech, or walking. • Swelling in your hands, ankles, or feet. • Unusual bleeding, bruising, or weakness. • Yellowing of your skin or the whites of your eyes.

Drug Generic Name (Trade Names)	Side Effects
Topiramate (Qudexy, Topamax) ¹	<ul style="list-style-type: none"> • Dermatologic: Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis • Endocrine metabolic: Hyperammonemia (Adolescents, 26%), Hypohidrosis, Increased body temperature, Metabolic acidosis (Adult, 14% to 44%; pediatric, 9% to 77%) • Hepatic: Liver failure • Neurologic: Drug-induced encephalopathy • Ophthalmic: Angle-closure glaucoma, Glaucoma, Myopia, Visual field defect (epilepsy, 0.1% to 1%) • Psychiatric: Suicidal thoughts • Renal: Nephrolithiasis (adults, 1% to 3%) • Other: Withdrawal sign or symptom • Neurologic: Confusion (3% to 11%), Dizziness (4% to 25%), Impaired cognition (2% to 7%), Impaired psychomotor performance (2% to 13%), Memory impairment (3% to 12%), Paresthesia (1% to 51%), Reduced concentration span (2% to 10%), Somnolence (6% to 29%)
Venlafaxine ² (Effexor)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Anxiety, restlessness, fever, sweating, muscle spasms, nausea, vomiting, diarrhea, seeing or hearing things that are not there • Blistering, peeling, red skin rash • Chest pain, cough, trouble breathing • Confusion, weakness, and muscle twitching • Eye pain, vision changes, seeing halos around lights • Fast or pounding heartbeat • Feeling more excited or energetic than usual • Headache, trouble concentrating, memory problems, unsteadiness • Seizures • Unusual behavior, thoughts of hurting yourself or others, trouble sleeping, nervousness, unusual dreams • Unusual bleeding or bruising
Verapamil ² (Calan, Covera-HS, Verelan)	<ul style="list-style-type: none"> • Extensive side effects noted: for full list see http://www.micromedexsolutions.com.ezp3.lib.umn.edu/micromedex2/librarian/PFDefaultActionId/evidenceexpert.DoIntegratedSearch# • Chest pain • Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes • Fast, slow, uneven, or pounding heartbeat • Lightheadedness, dizziness, fainting • Rapid weight gain, swelling in your legs, feet, or ankles • Trouble breathing • Unusual tiredness or weakness

*We did not differentiate between mild/moderate versus serious side effects.

Sources:

¹<http://www.micromedexsolutions.com>

²<https://www.ncbi.nlm.nih.gov/pubmedhealth/>

³<https://medlineplus.gov/>

Abbreviations: BP=bipolar disorder; FDA=United States Food and Drug Administration