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Effective Health Care Program

Treatment for Bipolar Disorder in Adults: A Systematic Review

Evidence Summary

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

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), dipolar 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]

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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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 week	Response Rate: Favors Cariprazine, OR 2.14 (95% CI 1.08, 4.23); NNT=5.6 Remission Rate: Favors Cariprazine, OR1.95 (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

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

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
	Haloperidol	Placebo

Table B. Interventions/comparators with insufficient strength of evidence (continued)

Category	Drug	Comparator
Mood Stabilizers for mania	Carbamazepine	Placebo
	Divalproex/Valproate	Placebo
	Valproate	No Placebo
	Lithium (for CGI only)	Placebo
	Carbamazepine	Lithium or Valproate
	Carbamazepine	Valporate
	Lamotrigine	Lithium
	Lithium	Haloperidol or Divalproex
Other Drugs for mania	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 (paraoxetine, bupropion, or both)	Placebo
	Sertraline	Lithium
	Venlafaxine	Lithium
	Lithium and OPT	OPT alone

Table B. Interventions/comparators with insufficient strength of evidence (continued)

Category	Drug	Comparator
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
	Valproic Acid plus Aripiprazole	Lithium plus Aripiprazole
	Venlafaxine	Lithium
	Ziprasidone and Mood Stabilizers	Mood Stabilizers alone (placebo)

Table B. Interventions/comparators with insufficient strength of evidence (continued)

Category	Drug	Comparator
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 – aripipravole, 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 Geriat 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 Psychiat 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. ohen M, Jacobs TG, Grundy SL, et al. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. The Olanzipine 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;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.

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