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Comparative Effectiveness Review
Number 62

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

Preface

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We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Treatment for Depression After Unsatisfactory Response to SSRIs

Structured Abstract

Objectives. A comparative effectiveness review was undertaken to evaluate treatment strategies in patients who failed to respond to selective serotonin reuptake inhibitors (SSRIs) as first-line treatment. The efficacy (benefits and harms) of monotherapy approaches (dose escalation, increased duration, or switch) or combined therapies were evaluated. Efficacy in the context of subgroups was also evaluated. Recommendations in Clinical Practice Guidelines (CPGs) from 2004 to April 2011 were compared.

Data Sources. MEDLINE®, Embase®, CINAHL®, PsychINFO®, AMED (Allied and Complementary Medicine), Cochrane Database of Systematic Reviews, and Cochrane Central® were searched from 1980 to April 13, 2011. An extensive grey literature search was also undertaken, including publications of drug regulatory agencies.

Review Methods. Systematic review methodology was employed. Eligibility criteria included English studies of adults (aged ≥18 years) or adolescents and children (8–18 years) with major depressive disorder, dysthymia, or subsyndromal depression, who had an inadequate response to an SSRI at entry into the study. Comparative study designs were eligible. Publications focusing only on treatment algorithms were not considered to be CPGs.

Results. From 46,884 citations, there were 44 studies and 27 guidelines that were eligible. Key Questions 1 and 2 (KQ1-a and KQ2): Forty-one studies included adults and three studies included adolescents; all included subjects with major depressive disorder except for one with adult dysthymia and subsyndromal patients alone. A limited number of studies (n=11) evaluated monotherapy strategies and these showed no differences among approaches. Although there were more studies evaluating monotherapy relative to combined therapies (n=33), the types of add-on agents were numerous and showed no relative differences; the exception was the addition of risperidone to an SSRI. KQ 3: Seven studies evaluated the impact of disease type, disease severity, previous comorbidities, age, gender, and race on treatment outcomes and showed no clear trend. KQ4: From 18 CPGs for adults, the majority did not provide specific recommendations for monotherapy strategies; for combination therapies, although specific agents were specified, there was variability across CPGs when recommending agents and strategies. Recommendations were more consistent for the CPGs for adolescents (n=7).

Conclusions. There is low strength of evidence evaluating relative differences for any monotherapy or combination therapy approach. All but 2 of 44 studies showed no relative differences in response and remission rates. Two studies with limited sample sizes and using risperidone as an augmenting agent showed benefit with combined therapy. The majority of studies were not designed to assess superiority of the strategies. Inconsistency and lack of clarity for clinical actions were noted when comparing CPGs.
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Executive Summary

Background

Depression is a complex mental illness associated with disability and reduced quality of life for the person with depression, as well as substantial societal burden. Major depressive disorder (MDD) is the second leading medical cause of long-term disability, the fourth leading cause of global burden of disease, and is predicted to become the second highest cause of disability by 2020.\textsuperscript{1,2} Depression exerts a negative impact on physical health; it reduces adherence to medical treatment,\textsuperscript{3} reduces participation in preventive activities,\textsuperscript{4} and increases the likelihood of risk factors such as obesity,\textsuperscript{5} smoking,\textsuperscript{6} and sedentary lifestyles.\textsuperscript{7} MDD may be associated with immune dysfunction\textsuperscript{8-11} and cardiovascular disease,\textsuperscript{12-15} endocrine and neurological diseases, and a general increase in chronic disease incidence.\textsuperscript{16} Mortality rates are high: approximately 4 percent of adults with a mood disorder die by their own hand, and about two-thirds of suicides are preceded by depression.\textsuperscript{17} In adolescents, untreated depression results in significant impairment in school performance, interpersonal relationships, risk of suicidal behavior and completion of suicide, risk of early pregnancy, occupational maladjustment, and impaired social and family functioning.\textsuperscript{18}

Pharmacological agents are one of several treatment modalities used for depression, and one of the most frequently utilized classes of antidepressant medications are the selective serotonin reuptake inhibitors (SSRIs). The rate of treatment response following first-line treatment with SSRIs is moderate, varying from 40 to 60 percent; remission rates vary from 30 to 45 percent.\textsuperscript{19} Up to one-third of persons taking antidepressant medications will develop recurrent symptoms of depression while on therapy.\textsuperscript{20} The target goal for acute treatment should be remission, which is defined as a resolution of depressive symptoms (a score within the normal range of the symptom scale). Response to treatment (usually defined as at least a 50 percent reduction in symptom levels\textsuperscript{21}) may not be sufficient as a target outcome because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcome.\textsuperscript{22} Clinicians are faced with a number of treatment options following an inadequate response to an SSRI, and these include monotherapy or combined therapy. Monotherapy options include: (1) an optimization strategy (increasing the dose or extending the duration of the SSRI), (2) switching to another SSRI, (3) switching to another class of antidepressants, or, (4) switching to a nonpharmacological intervention. Combination or add-on therapy options include: (1) combining the SSRI with an augmenting agent, (2) combining antidepressants, or (3) combining the SSRI with a nonpharmacological therapy (such as psychological therapies, exercise, etc.). It is also an option to switch to a new antidepressant and simultaneously combine that antidepressant with a second pharmacological or nonpharmacological treatment. This is sometimes referred to as an acceleration strategy.

Scope and Purpose of This Review

The primary goal of this comparative effectiveness review is to examine the evidence guiding clinical treatment decisions and ultimately to aid clinicians in their care of patients when SSRI therapy for an index episode does not result in an adequate treatment response. The Key Questions are as follows:
**Key Question 1.** Among adults and adolescents with major depressive disorder, dysthymia, and subsyndromal depression who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

**Key Question 1a.** How does efficacy/effectiveness vary among the different monotherapies and combined therapies?

**Key Question 2.** What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

**Key Question 3.** How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, age, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)? These subgroups will be considered with respect to the different interventions.

**Key Question 4.** What is the range of recommended clinical actions following the failure of one adequate course of an SSRI based on current clinical practice guidelines published between 2004 and April 2011?

**Methods**

**Search Strategy**

The search strategy was limited to studies published from 1980 to April 13, 2011, as SSRIs first became available for the treatment of depression in the early 1980s. The databases searched were: MEDLINE®, Cochrane Central®, PsychINFO®, Cochrane Database of Systematic Reviews, Embase®, CINAHL®, and AMED (Allied and Complementary Medicine). The grey literature search included systematic searches of relevant citations of Web sites: health technology assessment agencies (Hayes Inc. Health Technology Assessment), regulatory information (U.S. Food and Drug Administration, Health Canada, Authorized Medicines for European Community), clinical trial registries (ClinicalTrials.gov, Current Controlled Clinical Trials, Clinical Study Results, WHO Clinical Trials), grants and federally funded research (including National Institute of Health, Health Services Research Projects in Progress [HSRProj]), abstracts and conference proceedings (Conference Papers Index, Scopus), and the New York Academy of Medicine’s Grey Literature Index. Additionally, the sites of specialty organizations were searched for clinical practice guidelines (CPGs), and members of the Technical Expert Panel were queried for any additional guidelines of relevance. CPGs were limited to those published between 2004 and April 2011. Reference lists of eligible citations and systematic reviews were also searched for potentially relevant citations.

**Study Selection**

The study populations were eligible if they included adults (age ≥18 years of age) or adolescents (12 to 18 years of age) with MDD, dysthymia, or subsyndromal depression, who met the following criteria: (1) they were on SSRI treatment for the index episode at the time of entry into the study; (2) they have been judged to have had an “inadequate response” to an SSRI (fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, or paroxetine) at the time of entry into the study; or, (3) when recruited for entry into the study, they were to be placed on an SSRI for purposes of monitoring prospectively the adequacy of their response. Studies with subjects who failed to respond to a non-SSRI antidepressant or a nonpharmacological therapy or...
combination treatment were excluded. Subjects not receiving an SSRI at the time of entry into
the study, and not recruited to evaluate adequacy of response to an SSRI, were excluded. Studies
where the entire sample included subjects with postpartum depression, bipolar depression,
depressive psychosis, dysphoria, mourning syndrome, postoperative depression, premenstrual
dysphoric disorder, pseudodementia, puerperal depression, or seasonal affective disorder were
excluded. Similarly, studies where the entire sample were subjects with a cerebrovascular
accident, dementias (including Alzheimer’s disease, vascular dementia, mild cognitive
impairment), Parkinson’s disease, hypothyroidism, or Cushings’ syndrome were also excluded.

Experimental studies and observational studies with comparator groups were included in this
review. Study designs with no comparison group (e.g., case series, qualitative studies) were
excluded. There were no exclusions based on the types of pharmacological and
nonpharmacological interventions, with the exception of electroconvulsive therapy, vagal nerve
stimulation, and repetitive transcranial nerve stimulation.

The primary outcomes included remission (freedom or near freedom from symptoms; 100
percent change relative to baseline) and response (either partial, from 0 to 49 percent change
relative to baseline, or complete, from 50 to 99 percent change relative to baseline). Secondary
outcomes of interest included speed of response, relapse, quality of life, adherence, return to
work, global change as measured by global assessment scales, and external service utilization.

Data Extraction

Relevant fields of information were extracted from individual studies by trained data
extractors using standardized forms and a reference guide; a second reviewer verified the
accuracy of the data fields reported. Discrepancies were resolved by consensus or consultation.
Extracted data included study and population characteristics, eligibility criteria, types of
interventions and treatment specifications, and outcomes.

Assessment of Methodological Quality of Individual Studies

We selected the Risk of Bias Tool by the Cochrane Collaboration\textsuperscript{23} to assess randomized
controlled and controlled clinical trials. Studies were evaluated for adequacy of collecting and
reporting harms using the McHarm scale.\textsuperscript{24,25} The AGREE II instrument was used to assess the
methodological quality of the CPG.\textsuperscript{26}

Applicability

Applicability was assessed by establishing a priori the key attributes of the population (wide
spectrum of age [8 to 80 years], both genders, range of disease severity, range of the number of
previous failures), intervention (using antidepressants with established efficacy in standardized
doses), comparator, and outcome (standardized measures) in the context of a wider spectrum of
patients in primary care settings; that is, in the context of patients who would likely benefit from
these interventions in “real world” conditions. The findings of this review would not apply to
subjects who have a primary diagnosis of bipolar disorders, schizophrenia, or major anxiety
disorder.

Rating the Body of Evidence

The overall strength of the body of the evidence was assessed using four domains: (1) risk of
bias criteria; (2) consistency of results (degree to which study results for an outcome are similar
[variability is easily explained, range of results is narrow]); (3) directness of the evidence (assesses whether interventions can be linked directly to the health outcomes); and, (4) precision (degree of certainty surrounding an effect estimate for a specific outcome). The strength of the evidence is classified in one of four grades: high, moderate, low, or insufficient. Grading of the strength of evidence is applied to individual primary outcomes of benefit (response and remission and also harms [suicidality, weight gain, and sexual dysfunction]).

**Data Synthesis**

Qualitative synthesis was undertaken separately for adults and adolescents, and for MDD, dysthymia, and subsyndromal depression. Studies were grouped into three categories of treatment strategies that reflected clinical decisionmaking and these included: (1) monotherapy versus monotherapy, (2) monotherapy versus combined therapy, and (3) combined therapy versus combined therapy.

We evaluated the clinical diversity of the study interventions, populations, and outcomes when considering meta-analyzing studies; given the diversity of interventions and populations, summary estimates were not undertaken. Graphs presenting relative risk of individual studies within the various clinical groupings of interventions were prepared to examine differences of effect size.

**Results**

**Description of Eligible Studies and CPGs**

From an initial 46,884 citations, 3,147 were screened at full text, and a final set of 44 primary studies (74 publications) and 27 CPGs were eligible for this review. Publications that presented subgroup analyses, secondary analyses, reanalyses, results of different outcomes (not primary outcome measures), or results for different time points on the same study cohort were considered to be secondary records (or companion publications) to the original studies; as such, all STAR*D study publications are counted as a single study (with multiple publications).

**Key Question 1.** Among adults and adolescents with major depressive disorder, dysthymia, and subsyndromal depression, who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

**Key Question 1a.** How does the efficacy/effectiveness vary among the different monotherapies and combined therapies?

Forty-one studies (61 publications)\(^{28-88}\) included adults, and three studies (13 publications)\(^{89-101}\) included adolescents. One study evaluated subjects with subsyndromal depression\(^{79}\) and another with dysthymia;\(^{67}\) both of these studies showed no differences between groups when comparing monotherapy or combined therapy treatments. The findings for subjects with MDD are summarized below.
Monotherapy Versus Monotherapies in Adults

Twelve studies (18 publications) compared monotherapy interventions relative to other monotherapies. All participants (n=2,611) had MDD and were recruited almost exclusively from outpatient settings. The majority of subjects were white, female, and middle-aged (40 to 49 years). The interventions were a minimum of 4 weeks duration and three of the studies involved dose escalation of sertraline, venlafaxine, or paroxetine. The remaining eight studies (nine publications) evaluated head-to-head comparison following switching from: (1) citalopram to venlafaxine, bupropion, sertraline, or cognitive behavior therapy (CBT); (2) paroxetine to venlafaxine; (3) fluoxetine to olanzapine or mianserin; or (4) from an SSRI to duloxetine (tapering methods). As a group, these 11 studies are at moderate risk of bias across studies, with particular problems in randomization and the role of the funding agency. The findings suggest that there is no certainty of any advantage between different monotherapies (pharmacological or nonpharmacological) for either response to treatment or remission. The exception was a single study that showed that lower-dose sertraline had some small improvement in response, and that the frequency of adverse events decreased at the higher dose; this particular study also suggests that the differences may have been related to the longer trial duration as subjects were randomized after failure to respond to the lower dose. There is limited evidence to establish with certainty that a dose escalation or a switch to another antidepressant (SSRI or non-SSRI) is equivalent or superior to any comparator treatment in patients with inadequate response to an initial SSRI; our limited pool of studies would suggest that these monotherapies are equivalent in their treatment effects.

Strength of the Evidence for Monotherapies

When considering any monotherapy versus other monotherapy treatments in adults with MDD, the differing pharmacological and nonpharmacological interventions were considered as a single group, given that so few studies were eligible in this category. The studies generally showed no difference between groups. However, taking into consideration the moderate risk of bias, the imprecision, and the applicability of the populations, the evidence was graded as insufficient for both outcomes of benefit (response and remission); harms (suicidality, weight gain, and sexual dysfunction) were not measured or not reported in most studies, and as such were rated as having insufficient strength of evidence (SOE).

Monotherapies Versus Combined Therapies in Adults

A total of 33 studies (49 publications) evaluated the efficacy and effectiveness of monotherapy relative to combined therapies. Participants in the studies (n=4,537) were all diagnosed with MDD and recruited predominately from outpatient settings. The majority of subjects in these studies were middle-aged females of the white race (when ethnicity was reported). Fifteen studies (18 publications) determined failure of response to the SSRI prospectively and 16 retrospectively (18 publications). No studies evaluated subjects specifically for failed response to fluvoxamine alone. All but one study employed a randomized controlled trial (RCT) design, and all studies included a pharmacological intervention for at least one treatment arm. The majority of studies employed a study design that had the comparator arm receive ongoing treatment with an SSRI to which the subjects had not had an adequate response by the start of the study; fewer studies employed a design in which patients were switched to a new treatment in at least one study arm.
Four studies had one treatment arm that evaluated a combination therapy that included the non-SSRI antidepressants clomipramine, bupropion, or desipramine. Twenty-six of 33 studies evaluated combination therapies that included augmenting agents. From these, only five augmenting agents were evaluated in two or more studies; these included atypical antipsychotics (olanzapine and risperidone), lithium, mianserin, and pindolol. Five studies evaluated the use of nonpharmacological interventions including CBT, dialectical behavior therapy, interpersonal therapy, and exercise. Method of randomization, compliance with treatment, and the role of the funder were at high risk of bias for over 75 percent of these studies. Eighteen studies (22 publications) were funded solely by industry, ten (13 publications) by non-industry sources, and one by both. Overall, these studies were rated as having moderate risk of bias. Inadequate sample size was a factor in many studies.

The majority of studies showed no certainty of any difference for any monotherapy treatment, relative to the comparator combined therapy, for the outcomes of response and remission. The exception was with the atypical antipsychotics (olanzapine, risperidone, aripiprazole, quetiapine) used as augmenting agents, which showed small differences favoring the combination therapy. Overall, there is limited supportive evidence for any single augmenting drug or for switching to a different antidepressant (monotherapy) relative to adding another treatment (pharmacological or nonpharmacological).

SOE for Monotherapies Versus Combined Treatment

The SOE for the studies evaluating monotherapies relative to combined therapies had more eligible studies that were categorized into distinct intervention groups. When considering augmenting agents as a single group, the studies were at moderate risk of bias, inconsistent, and imprecise, and as such both the outcomes of benefit and harm were rated as of insufficient SOE. We also partitioned the studies into relevant subgroups based on the type of augmenting agent (atypical antipsychotics, buspirone, lithium, or mianserin). With the exception of atypical antipsychotics (low SOE) and switching to buspirone (low SOE), all other groupings for the different augmenting agents were given a rating of insufficient for evaluating both the outcomes of benefit and harm. When considering the grouping of interventions into those where switching to a new agent (monotherapy) was compared with switching and adding another treatment (such as a new SSRI, non-SSRI, or nonpharmacological treatment), the SOE was graded as low. The STAR*D trial contributed to many of the comparisons and affected the final grade in this treatment category.

Combined Therapies Versus Combined Therapies in Adults

There were six studies for which there were treatment arms that compared combination therapies with each other. All but one study were RCTs. Women were the majority in all studies, and age ranges varied from 37 to 59 years. Only two studies reported racial composition, and these subjects were predominately white. Two studies compared different doses of the same combination drug therapies (ziprasidone and lithium). In addition to SSRIs, added therapies included lithium, desipramine, buspirone, bupropion, citalopram, clomipramine, or CBT. Overall, these studies were rated as having a moderate risk of bias, with problems in randomization, reporting compliance, and balancing prognostic indicators between groups. Adequate sample size was an issue in these studies. There was no certainty of a
difference between any combination therapy, including a dose escalation, for the added augmenting agent.

**SOE for Combined Therapies**

All interventions within the combined therapies relative to other combined therapies were grouped as one category for grading SOE; the overall grade was assigned as insufficient for both the outcomes of benefit and harm due to serious risk of bias, inconsistency, and imprecision.

**Treatment in Adolescents**

Two studies (trials) evaluated therapies in children and adolescents who had failed to respond to a previous SSRI; one trial of patients ages 12 to 18, and a second trial of ages 8 to 18. In the Treatment for Resistant Depression in Adolescents (TORDIA) trial, the majority of the sample (68 to 72 percent) were girls, with an average age of 16 years. Study subjects were randomized to four treatment arms that included venlafaxine alone or combined with CBT, or a switch to an SSRI (citalopram, fluoxetine, or paroxetine) alone, or with CBT. This study was at low risk of bias. The trial stated that it aimed to demonstrate the superiority of venlaxafine, but the findings failed to reject the null hypothesis showing no differences between the medication groups. There was a statistically significant difference in favor of including CBT for all outcomes, however. The second trial evaluated a dose escalation of fluoxetine in a small sample, and was suggestive of some benefit to the higher dose, but the study was underpowered to detect a difference.

**SOE for Adolescent Studies**

SOE was evaluated for the findings from the TORDIA trial alone. This trial had low risk of bias, and harms were well monitored and reported. The SOE was rated as low due to the potential imprecision of this study.

**Key Question 2. What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?**

Harms for interventions used for both adults and adolescents with MDD who had failed to respond to an SSRI were predominately derived from RCTs that evaluated treatment strategies in this population. No observational studies met the eligibility criteria. A clear trend for harms was difficult to specify across the differing interventions in adults. In general, the majority of harms reported were consistent with those associated with antidepressant use and were likely mild to moderate in nature.

With the exception of the studies evaluating children and adolescents, the reporting and collecting of harms was problematic, particularly for predefining harms (e.g., nausea for >1 day), including serious and severe events, and for reporting the total number of events per group in studies with adults. The two studies evaluating adolescents provide good evidence for harms within this population as they were generally at low risk of bias. In studies with adult MDD populations, severe events and serious events such as suicidality were reported inconsistently. A limited number of studies undertook statistical evaluation comparing harms between groups.
Key Question 3. How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, age, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)? These subgroups will be considered with respect to the different interventions.

Seven studies undertook stratified or subgroup analyses evaluating factors that may impact treatment outcomes in adults, and one for adolescents. The effects of baseline severity, previous treatment failure, age, gender, and race were not sufficiently evaluated and were inconsistent in their impact on outcomes in adults. There is some evidence from the STAR*D level 2 cohort that would suggest that persons with concurrent anxiety symptoms have less likelihood of achieving remission. There is some evidence from the TORDIA trial that milder depression, less family conflict, and the absence of suicidal behavior are associated with greater likelihood of a positive treatment response to combined therapy at 12 weeks in adolescents. A history of physical and sexual abuse may predict response to combined therapy in adolescents.

Key Question 4. What is the range of recommended clinical actions following the failure of one adequate course of SSRI based on current clinical practice guidelines published between 2004 and April 2011?

There were a total of 27 CPGs sponsored by unique organizations and described in 33 publications. Seven CPGs were specific only to adolescents, 18 CPGs were for adults alone, and 2 CPGs were applicable to both. Four CPGs for adults and three for adolescents did not provide any recommendations for patients with previous inadequate responses. Five of the 27 guidelines included patients with dysthymia and subsyndromal depression but none of the recommendations were for patients with this diagnosis who had failed to respond to previous treatment (pharmacological or nonpharmacological). The majority of CPGs did not specify a definition for inadequate response. All CPGs were applicable to patients from primary care and outpatient settings. The domains within the AGREE II showed great variability in the scores, suggesting significant differences amongst the CPGs. Domains with the greatest variability included domain 3 (rigor of development), domain 5 (applicability), and domain 6 (editorial independence). For adults, increasing the dose or duration was frequently recommended (often a first approach), but the interval or change in dose was not specified. The majority of CPGs did not recommend any specific type of antidepressant when recommending switching to monotherapy strategies. When combination therapy was recommended, there was a greater tendency to specify the drug for adding to the antidepressants. However, there was great variability in the augmenting agents recommended. For adolescents, there was an approximately equal number of CPGs that specified the agents to consider for monotherapy and for combined therapies. Many CPGs expressed a preference to commence treatment using nonpharmacological approaches prior to pharmacological treatment in this population. Some adolescent guidelines cited adult evidence as the evidentiary basis for suggesting treatment strategies.
Recommendations for Future Research

1. Future trials should specify a priori the intent of the trial as establishing either equivalence, noninferiority, or superiority of the head-to-head comparisons. Justification for the margin of inferiority or superiority should be specified. Ideally, designing trials to establish superiority is preferred, as this may assist clinicians in selecting amongst competing treatment strategies. Similarly, in studies designed to involve a population of patients who have failed to respond to treatment, determining this failure in a prospective manner as the first part of a two-part study, rather than simply asking patients about failure, confers methodological advantages with regard to minimizing bias and allowing disentanglement of the reasons for failure (adverse events, compliance, or physiological response). Sample sizes in future research studies should be sufficient to establish important margins of difference between groups and to evaluate potentially important confounders, such as age, gender, and baseline severity.

2. Future research should include a broader representation of adult patients with respect to age (>50 and <40 years), gender (equal proportion of men), and ethnicity (increased proportion of nonwhite or non-Caucasian, or broader representation of all ethnic groups). Similarly, a broader representation of participants with the medical or psychiatric comorbidities typically found in the primary care setting should be included.

3. Studies should be more consistent in reporting the manner for determining previous history of failed treatment trials and past episodes of depression.

4. There is a need to increase the number of studies including subjects with dysthymia and subsyndromal depression who have failed to respond to previous SSRI treatments.

5. There is also a need to increase research in children (ages 8 to 12 years) and adolescents (ages 12 to 18 years).

6. Trials of new add-on treatments for patients not responding to an antidepressant medication have not examined whether the add-on agent is equally effective when added to a range of antidepressant classes. There appears to be an assumption among investigators in this field that response and remission will be comparable regardless of the class of background medication; the clinical or neurobiological data to support this assumption should be confirmed or revisited.

7. Future clinical trials should conform to CONSORT134 (Consolidated Standards of Reporting Trials) reporting standards for harms. Severe and serious events (including suicidality) were inconsistently reported and improvement is necessary in this area.

8. Development of future CPGs for adolescents or adults should provide a clear definition of inadequate response for both pharmacological and nonpharmacological treatments, and should include standardized methods for establishing this in “real world” settings. Future CPG recommendations should provide greater clarity with regards to recommended treatment actions and should make clear the link between the recommendation and the evidence.

Conclusions

Studies in adults with MDD who have had an inadequate response to an SSRI included a preponderance of subjects with multiple past depressive episodes and multiple past unsuccessful treatment trials. The generalizability of these data to people with few past episodes of depression and few past unsuccessful treatments for depression may be limited. In addition, these studies
included a high proportion of caucasians and women, and tended to have an average patient age in the early forties. Studies are needed with a sufficient sample size to explore whether there are differences in race, gender, or across the age spectrum.

The number of studies comparing single medications against each other (monotherapy compared with monotherapy) following an inadequate response to an SSRI are few and evaluate different agents. Extant studies are limited in type of agents utilized, sample sizes, and population characteristics. There is insufficient evidence to determine whether there is a difference between various single-agent therapies in the outcomes of response and remission following an inadequate response to an SSRI.

There is insufficient evidence to evaluate the benefits of ongoing monotherapy with an SSRI compared with combination treatment involving the addition of another antidepressant medication to the initial SSRI. There is low-grade evidence that comparable results are achieved following the switch to an alternate antidepressant medication (monotherapy with a new antidepressant) when compared with adding a nonantidepressant treatment to the initial SSRI (traditional augmentation approach). There is low-grade evidence that adding an atypical antipsychotic medication to ongoing SSRI treatment is associated with higher response and remission rates compared with adding a placebo to ongoing SSRI treatment (following inadequate response to the SSRI). There is insufficient evidence to confirm that there is an improvement in response and remission rates following the addition of any other augmentation agents. There is insufficient evidence to evaluate the benefits or harms of specific combinations of treatments relative to alternative combinations. There is a single study evaluating patients with subsyndromal symptoms and dysthymia who had had an inadequate response to SSRI medications; the evidence base is limited in these populations.

There are three studies evaluating children and adolescents. Only one study provided evidence to support the use of CBT in combination with an antidepressant following inadequate response to an SSRI for adolescents ages 12 to 18 years with MDD. A second study, a pilot with small sample size evaluating dose escalation, showed no effect.

A clear trend for harms was difficult to specify across the differing interventions in adults, although there were some studies (particularly for children and adolescents) where harms were well evaluated and clinically important differences between treatment groups were not apparent. The reporting and collecting of harms was problematic, particularly for predefining harms, including serious and severe events and reporting the total number of events per group in studies with adults.

The majority of CPGs for adults were applicable to patients with MDD in outpatient and primary care settings. Most CPGs did not specify definitions of “inadequate response” but did provide suggestions for treatment approaches. Recommendations for monotherapy (including dose or interval changes, switching to a different SSRI, or to a non-SSRI) were nonspecific as to the drug, interval, or dose change. Recommendations for combination therapy tended to endorse switching or adding different classes of antidepressants and augmenting agents. However, there was inconsistency across CPGs with regard to the types of augmenting agents to use. The variation amongst CPGs reflects the limitations of the evidentiary base.
References


69. Licht RW, Qvitza S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacol. 2002;161(2):143-51. PMID:11981594


112. Ravindran AV. If a patient does not respond to a full dose of fluvoxamine for at least 12 weeks, what alternatives should be considered? J Psychiatry Neurosci. 1998;23(2):136 PMID:9549254


Introduction

Background

Depression is a complex mental illness that is associated with disability and reduced quality of life for the person with depression, as well as substantial societal burden. Pharmacological agents are one of several treatment modalities used for depression and one of the most frequently utilized classes of antidepressant medications are the selective serotonin reuptake inhibitors (SSRIs). The rate of treatment response following first-line treatment with SSRIs is moderate, however, varying from 40 to 60 percent; remission rates vary from 30 to 45 percent.\(^1\) Up to one third of persons taking antidepressant medications will develop recurrent symptoms of depression while on therapy.\(^2\) The definition of an adequate response to SSRI medications is not consistently operationalized, but it is generally accepted that a 50 percent decrease in symptom severity constitutes a response.\(^3\) Remission from depression is defined as being free or nearly free of symptoms for the current episode. This review evaluates treatment options for patients who fail to improve fully, who only improve partially, or who have no response to an SSRI medication.

Epidemiology of Depression in Adults and Adolescents

Major depressive disorder (MDD) is the occurrence of one or more major depressive episodes (MDE). An MDE is defined as a period of at least 2 weeks that is characterized either by depressed mood and/or markedly diminished interest or pleasure in all, or almost all, activities in addition to at least four other symptoms.\(^4\) Dysthymic disorder is characterized by a chronically depressed mood and at least two other depressive symptoms that occur most of the day, more days than not, for at least 2 years. The Diagnostic and Statistical Manual, 4\textsuperscript{th} edition, Text Revision (DSM-IV-TR) includes specifiers that can be used to further describe the characteristics of MDE or dysthymic disorder, such as whether an episode of depression includes psychosis or occurs in the postpartum period. The operational definition for subsyndromal depression was defined by Judd\(^5\) for individuals who do not meet criteria for a diagnosis of minor depression, major depression, and/or dysthymia. The definition specifies the presence of two or more simultaneous symptoms of depression associated with evidence of social dysfunction for most or all of the time for at least 2 weeks. Depression is common in adults and adolescents and is characterized by chronic, recurrent episodes that have significant impact on disability and mortality.

There is increasing acceptance that symptoms that do not meet the full criteria for MDD, but that are persistent, may cause distress and disability in persons with these symptoms. The DSM-IV-TR describes two related subthreshold categories of dysthymia and minor depression. dysthymia is characterized by an overwhelming yet chronic state of depression, exhibited by a depressed mood for most of the days, for more days than not, for at least 2 years. In children and adolescents, mood can be irritable and duration must be at least 1 year. A person who suffers from this disorder must not have gone for more than 2 months without experiencing two or more of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, or feelings of hopelessness. In addition, no MDD episode has been present during the first 2 years (or 1 year in children and adolescents) and there has never been a manic episode, a mixed episode, or a
hypomanic episode, and criteria have never been met for cyclothymic disorder. Further, the symptoms cannot be due to the direct physiological effects of the use or abuse of a substance such as alcohol, drugs or medication, or a general medical condition. The symptoms must also cause significant distress or impairment in social, occupational, educational, or other important areas of functioning.

**Prevalence of Depressive Disorders**

Kessler reported estimates of 16 percent lifetime prevalence and 7 percent annual prevalence of depression in the United States for adults. These are slightly higher than European prevalence rates of 13 percent lifetime and 4 percent annual. European estimates of the prevalence of dysthymic disorder in adults based on DSM-IV-TR criteria, are 4 percent lifetime and 1 percent annual. Despite increases in provision of treatment for people with depression, a reduction in prevalence has not yet been discernable in those countries where before–after comparisons have been feasible. This may be in part because a substantial number of people with depression remain untreated or receive inadequate treatment. The Netherlands Mental Health Survey and Incidence Study assessed episode duration in community residents with new-onset episodes. Although 50 percent of people recovered within 3 months, the recovery rate flattened over time, and the authors estimated that approximately 20 percent would have episodes lasting longer than 24 months.

The prevalence of MDD in adolescents, 12 to 16 years of age, varies from 4 to 8 percent. There is an increased risk of depression following puberty, especially in girls relative to boys (2:1 ratio). Prevalence of MDD among adolescents has been reported to be as high as 20 percent. Although the literature is limited, the few studies that evaluate dysthymia in adolescents report disease prevalence varying from 1.6 percent to 8.0 percent. Adolescents with depression have high rates of comorbid psychiatric conditions (reports vary from 40 to 90 percent), including anxiety, attention deficit hyperactivity disorder and substance abuse problems.

**The Disease Burden Associated With MDD, Dysthymia**

MDD is a leading cause of disability across the world. Specifically, depression is the second leading medical cause of long-term disability and the fourth leading cause of the global burden of disease, predicted to become the second highest cause of disability by 2020. The ongoing transition to a knowledge-based economy is expected to further magnify the impact of MDD on occupational functioning. Depressive disorders negatively affect quality of life (QOL); 63 percent of respondents with MDD had severe impairment in QOL, while 85 percent of those with double depression (MDD and dysthymic disorder) and 56 percent of those with dysthymic disorder had QOL impairment in the severe range. The economic burden of depressive disorders is estimated to be $83.1 billion per year.

The National Comorbidity Survey Replication study in the United States found that role impairment in people with MDD was lowest in the occupational domain and highest in the social domain. About 60 percent of respondents with an MDE in the past year reported severe or very severe role impairment. Parental depression has a negative effect on the development of their children and on family dynamics and intergenerational effects may amplify the impact of depression on population health.

Depression also has a negative impact on occupational functioning. In one study, depressed workers had significantly greater performance deficits than control workers who had rheumatoid
arthritis, with regard to performing mental tasks, time management, output tasks, and physical tasks. When depressed workers were compared to workers with rheumatoid arthritis, the depressed employees were almost five times as likely to become unemployed than those with arthritis. Depressed employees are also more likely to become unemployed or miss time at work than physically ill employees.

Depression exerts a negative impact on physical health; it reduces adherence to medical treatment, reduces participation in preventive activities, and increases the likelihood of risk factors such as obesity, smoking, and a sedentary lifestyle. MDD may be associated with immune dysfunction, cardiovascular disease, endocrine and neurological diseases, and a general increase in chronic disease incidence. Mortality rates are high; approximately four percent of people with a mood disorder die by their own hand and about two thirds of suicides are preceded by depression.

In adolescents, untreated depression results in significant disability in school performance, interpersonal relationships, risk of suicidal behavior and completion of suicide, risk of early pregnancy, occupational adjustment, and impaired social and family functioning.

Clinical Assessment, Management, and Response

Depression is frequently underdiagnosed in primary practice in both adults and adolescents. The World Health Organization (WHO) Psychological Problems in General Health Care study reported that primary care physicians diagnosed only 42 percent of adult patients with major depression. Possible benefits of screening and diagnostic tools to improve detection of depression in primary practice have been examined. Several tools are available for monitoring of depressive symptoms and there were no major differences between these instruments in a comparative study. The Patient Health Questionnaire-9 item (PHQ-9) or the Quick Inventory of Depressive Symptoms–Self Report (QIDS-SR) appear to be increasing in use, perhaps because of their brevity and strong alignment with DSM-IV-TR. The spectrum of depressive morbidity encountered by primary care physicians is broad. There is also recent evidence suggesting that diagnosis of depression in primary care may not be the major barrier to successful treatment; rather, it may be that patients are not receptive to suggested treatment for a condition that was not the reason for the visit to the physician. In primary care, the range of interventions offered may extend from close monitoring of mild episodes without immediate treatment (watchful waiting), through guided self-management, brief psychological or behavioral interventions, pharmacological management, and, if needed, referral to more specialized services or hospital admission.

Phases of Treatment of Major Depressive Episodes

Based on the work of Kupfer, treatment for MDD is commonly divided into three phases: acute, continuation, and maintenance. Acute treatment is aimed at the elimination of symptoms of depression and the restoration of psychosocial functioning. Continuation is a prolongation of treatment from four to nine months, such that the episode of depression is considered completely resolved. For the continuation phase, the treatment aims to return patients to baseline function and quality of life, and to prevent recurrence of symptoms. For the maintenance phase when symptoms have been resolved, the treatment goal is to prevent recurrence of new episodes of MDD. In this context, relapse is understood to occur during the continuation phase, but recurrence during the maintenance phase.
The target goal for acute treatment should be remission, which is defined as a resolution of depressive symptoms (score within a normal range of the symptom scale). Response to treatment, usually defined as at least a 50 percent reduction in symptom levels, may not be sufficient as a target outcome because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcome.

**Duration of First-Line Treatment Prior To Establishing Adequate Response**

Embedded within the decision that a patient has not had an adequate response to treatment, is the issue of defining an adequate duration for that treatment. Antidepressant effect may begin within 1 to 2 weeks of initiation and early improvement is a prognostic factor for remission. In STAR*D, 93 percent of patients first achieved response after 8 or more weeks, while 41 percent of patients who ultimately remitted first attained remission between 4 and 8 weeks after initiating treatment.

Some guidelines suggest that patients with at least minimal improvement (≥20 percent improvement in scores on a depression rating scale after four to six weeks) should continue with the antidepressant for another two to four weeks before considering additional strategies. The American College of Physicians (ACP) recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy for MDD.

**Outcomes of Importance**

There are a number of outcomes that are used within primary care and psychiatry to assess and monitor response to treatment. These scales include those that are self-report or completed by the clinician. Outcome assessment is usually conducted using validated interviewer-rated scales such as the Hamilton Depression Rating Scale (HAMD) or the Montgomery Åsberg Depression Rating Scale (MADRS). Although limitations have been recognized to the use of the HAMD in outpatient populations, it remains widely used. Response is typically defined as ≥50 percent reduction in scores on these scales, while remission is defined as a score within the normal range. However, despite a number of well-validated instruments to assess depression symptoms, there is some suggestion that physicians in primary care may not routinely use these; based on qualitative analyses, factors that influenced the use of these standardized assessments were time constraints, clinician familiarity with the instrument, and lack of clinical evidence. There is also some evidence that primary care physicians have a sensitivity varying from 48 to 50 percent when ruling in depression using unassisted methods (without the use of severity scales, diagnostic instruments, educational programs, or other organizational approaches).

**Defining Inadequate Response and Estimates Within the Population**

Subjects who are classified as having failed treatment or as having an “inadequate response” are eligible for this review. Treatment failure subjects would ideally be defined as those subjects who are currently on SSRI treatment for the index episode at the time of entry into the study. At that point these subjects have been judged to have had an “inadequate response” at the time of entry into the study or just prior to randomization. An “inadequate response” is typically established using a standardized instrument, where the scores relative to baseline reflect an improvement of less than 50 percent. The term “inadequate response” is therefore
synonymous with terms such as “nonresponders,” “failure to respond,” and “treatment failure.” These terms primarily reflect the perspective of the clinician or researcher. Partial response refers to a change in baseline score from 25 to 49 percent. Nonresponse is defined as less than 25 percent change in baseline score.

The rate of treatment response following treatment with SSRIs is moderate, varying from 40 to 60 percent.\(^1\) Up to two thirds of adult patients will not achieve remission with SSRI treatment.\(^2\) Up to one third of adults on drug treatment will develop recurrent symptoms of depression while on therapy.\(^2\) Moreover, there is limited evidence identifying reliable predictors (demographic, clinical, or genetic characteristics) of individual response.\(^3\)

Within their systematic review evaluating the efficacy of treatment for adolescents, Williams, et al.,\(^4\) showed that the rates of children failing to respond to an initial trial of SSRIs varied from 31 to 64 percent in eligible studies. Similarly, up to 60 percent of adolescents placed on combined treatment for depression (including pharmacological and behavioral therapies) respond positively to these interventions.\(^4\)

A portion of patients who have experienced an inadequate response from a clinical perspective may also go on to be defined as treatment resistant if they also fail to respond to subsequent treatment strategies. Treatment resistance is variably defined but usually refers to patients who have failed at least two trials of medication that have been of adequate dose and duration.\(^5\) Some definitions suggest that the failures should be to medications of different classes, but this is not universally accepted.

Monitoring adherence to antidepressants is sometimes difficult, but nonadherence may account for up to 20 percent of patients classified as having treatment resistant depression.\(^6\) Similarly, there is the potential for pseudoresistance or nonresponse to inadequate treatment. All this would suggest the difficulty of defining and capturing subjects who have had treatment failure and related subgroups. It may also reflect heterogeneity across studies evaluating the efficacy of SSRIs within this patient population.

### Treatment After an Inadequate Response

Treatment strategies following an inadequate response to an SSRI vary and can include monotherapy or combined therapy. Monotherapy options include: (1) an optimization strategy (increasing the dose or extending the duration of the SSRI), (2) switching to another SSRI, (3) switching to another class of antidepressants, or (4) switching to a nonpharmacological intervention. Combination or add-on therapy options include: (1) combining the SSRI with an augmenting agent, (2) combining antidepressants, or, (3) combining the SSRI with a nonpharmacological therapy.\(^7\) It is also an option to switch to a new antidepressant and simultaneously combine that antidepressant with a second pharmacological or nonpharmacological treatment. This is sometimes referred to as an acceleration strategy.

### Evaluation of Current Clinical Practice Guidelines for Inadequate Response

Recognizing that clinicians have a number of treatment options when addressing patients with an inadequate response, we thought it would be important to identify and evaluate current recommendations within current guidelines regarding the optimal approach to treatment. Our goal was to critically appraise these current guidelines and compare any differences in recommendations.
Scope and Purpose of this Review

A variety of treatment strategies aimed at helping individuals who have inadequate responses to SSRIs have been studied in patients with depression. The primary goal of this comparative effectiveness review (CER) is to examine the evidence guiding clinical treatment decisions and ultimately to aid clinicians in their care of patients when SSRI therapy for an index episode does not result in an adequate treatment response. The Key Questions are as follows:

**Key Question 1.** Among adults and adolescents with major depressive disorder (MDD), dysthymia, or subsyndromal depression who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

**Key Question 1a.** How does the efficacy/effectiveness vary among the different monotherapies and combined therapies?

**Key Question 2.** What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

**Key Question 3.** How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, ages, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)? These subgroups will be considered with respect to the different interventions.

**Key Question 4.** What is the range of recommended clinical actions following the failure of one adequate course of SSRI based on clinical practice guidelines published between 2004 and April 2011?
Methods

Topic Development

The topic of this report and preliminary Key Questions (KQs) were developed through a participatory process involving the public, the Scientific Resource Center for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ), and various stakeholder groups. We communicated with eight key informants who represented psychiatrists, primary care practitioners, consumer representatives, and researchers in the area when formulating the research questions. Additional study, patient, intervention, and eligibility criteria, as well as outcomes, were refined and agreed upon through discussions between the McMaster University Evidence-based Practice Center, the Technical Expert Panel (TEP) members, the AHRQ Task Order Officer (TOO), a patient representative, and comments received from the public. Upon completion of the topic refinement, the key questions were posted for public comment, which were then summarized and discussed with the TEP. Relevant modifications (additions or clarifications) were incorporated.

Analytic Framework

Following consultation with key informants, the AHRQ TOO, and the investigative team, the key research questions were developed. Figure 1 shows a flow diagram indicating the relationship between research questions in this CER. The first box in the figure shows the last question (KQ4) where clinical practice guidelines (CPGs) are evaluated. The other research questions are related to interventions used following the inadequate response to a selective serotonin reuptake inhibitors (SSRIs) for the index episode of depression. The treatment options following a failed response include the seven options (defined as interventions) for KQ1. Harms associated with any of these interventions are evaluated in KQ2 and can include suicide, sexual dysfunction, gastrointestinal effects, and neuropsychiatric effects. The study effects are evaluated in KQ1, KQ2, and KQ3, with the latter question considering subgroups related to different populations with depressive symptoms and other related factors potentially impacting treatment response. We note that intermediate outcomes, such as response and remission, may precede quality of life or societal outcomes.
Figure 1. Analytic framework

(KQ 4)
- Review of CPGs

Patients with unsatisfactory response to SSRIs as first-line therapy for depression

(KQ 2)
- Suicide
- Suicidality
- GI side effects
- Neuropsychiatric side effects
- Cardiac side effects
- Sexual side effects

(KQ 1, 3)
- Partial or full response
- Remission

- Improved function
- Improved quality of life
- Decreased health care utilization
- Increased return to work

(KQ 4)
- Change the dose or duration of the same SSRI
- Change to another SSRI
- Change to another class of antidepressant
- Change to nonpharmacologic therapies
- Add an augmenter (such as lithium)
- Add a second SSRI or antidepressant from another class
- Add various nonpharmacologic therapies

CPG = clinical practice guideline; GI = gastrointestinal; KQ = Key Question; SSRI = selective serotonin reuptake inhibitor
Search Strategy

For the primary studies, the search strategy was delimited to studies published from 1980 to April 13, 2011, as SSRIs first became available for treatment of depression in the early 1980s. The following electronic bibliographic databases were searched: MEDLINE®, Cochrane Central®, PsychINFO, Cochrane Database of Systematic Reviews, Embase®, CINAHL®, and AMED. The strategies used combinations of controlled vocabulary (medical subject headings, keywords) and text words. Appendix A details the strategies used to capture relevant citations. For the CPGs, the search was limited to those published from 2004 to April 2011.

A grey literature search was undertaken by the AHRQ Scientific Resource Center and identified potentially relevant citations or information by searching the Web sites as follows:

1. Health Technology Assessment agencies (Hayes Inc. Health Technology Assessment),
2. Regulatory information (United States Food and Drug Administration [FDA], Health Canada, Authorized Medicines for European Community),
3. Clinical trial registries (clinical.trials.gov, Current Controlled Clinical Trials, Clinical Study Results, WHO Clinical Trials),
4. Grants and federally funded research (National Institutes of Health, Health Services Research Projects in Progress [HSRProj]),
5. Abstracts and conference proceedings (Conference Papers Index, Scopus), and,
6. The New York Academy of Medicine’s Grey Literature Index. Additionally, the sites of specialty organizations for CPG were searched and members of the TEP were queried for potentially relevant guidelines.

Review of reference lists of systematic reviews published from 2005 forward was also undertaken. Similarly, the reference lists of eligible studies at full text screening were reviewed for relevant references. Any potentially relevant citations were cross-checked with our citation database and any that were new were retrieved and screened at full text.

Study Selection

Types of Participants

Subjects who are classified as having failed treatment or as having an “inadequate response” were eligible for this review. Treatment failure subjects would ideally be defined as those subjects who are currently on SSRI treatment for the index episode at the time of entry into the study. At that point these subjects have been judged to have had an “inadequate response” at the time of entry into the study or just prior to randomization. An “inadequate response” is typically established using a standardized instrument, where the scores relative to baseline reflect an improvement of less than 50 percent. The term “inadequate response” is therefore synonymous with terms such as “nonresponse,” “failure to respond,” and “treatment failure.” These terms primarily reflect the perspective of the clinician or researcher. Partial response refers to a change in baseline score from 25 to 49 percent. “Nonresponse” is defined as a change in baseline score of less than 25 percent. For this CER, the term “unsatisfactory response” was used to reflect the patient’s perception of their response to the intervention to treat their depression.

Specific eligibility is as follows: the study populations were eligible if they included adults (≥18 years) or adolescents (12 to 18 years) with major depressive disorder (MDD), dysthymia, or subsyndromal depression, who meet the following criteria:
• Currently on SSRI treatment for the index episode at the time of entry into the study,
• Have been judged to have had an “inadequate response” at the time of entry into the study (by any method),
• The SSRIs that patients did not respond to as a first-line therapy include the following: fluoxetine, citalopram, fluvoxamine, sertraline, escitalopram, and paroxetine,

OR
• The subjects who are recruited for entry into the study are to be placed on an SSRI for purposes of monitoring prospectively the adequacy of their response; subsequent evaluation includes an intervention for those that have been shown to not respond adequately to the SSRI.

Exclusion
The study populations were not eligible if adults (>18 years) and adolescents (12 to 18 years) with MDD, dysthymia, or subsyndromal depression met the following criteria:
• Are not receiving an SSRI at the time of entry into the study (including studies that included antidepressants but were not stratified for an SSRI subgroup),
• Are not recruited to evaluate the adequacy of response prospectively,
• Have post-partum depression, bipolar depression, depressive psychosis, dysphoria, mourning syndrome, postoperative depression, premenstrual dysphoric disorder, pseudodementia, puerperal depression, seasonal affective disorder,

OR
• Populations for whom the patho-physiological mechanism of depression is not comparable to those diagnosed with MDD, including patients having initially sustained a cerebrovascular accident, who suffer from dementias (including Alzheimer’s disease, vascular dementia, mild cognitive impairment), Parkinson’s disease, hypothyroidism, or Cushing’s syndrome

Types of Interventions
For KQs 1 to 4, the pharmacological and nonpharmacological interventions of interest are as follows:

Selective-Serotonin Reuptake Inhibitors (SSRIs): Fluoxetine (Fluoxetine Hydrochloride, Prozac, Prozac Weekly, Sarafem, Symbax), Citalopram (Celexa, Citalopram Hydrobromide), Fluvoxamine (Fluvoxamine Maleate, Luvox, Luvox CR), Sertraline (Sertraline Hydrochloride, Zoloft), Paroxetine (Paroxetine Hydrochloride, Paxil, Paxil CR, Pexeva), Escitalopram (Escitalopram, Escitalopram Oxalate, Lexapro).

NonSSRI Antidepressants: Duloxetine Hydrochloride (Cymbalta), Venlafaxine (Effexor, Effexor XR, Pristiq), Desvenlafaxine Succinate (Pristiq), Phenelzine Sulfate (Nardil), Tranylcypromine Sulfate (Parnate), Emsam (Selegiline), Moclobemide (Manerix), Doxepin (Sinequan, Zonalon, Doxepin Hydrochloride), Clomipramine (Anafranil, Clomipramine Hydrochloride), Amitriptyline (Amitid, Amitril, Elavil, Endep, Etrafon 2-10, Etrafon 2-25, Etrafon-a, Etrafon-Forte, Limbitrol, Limbitrol DS, Perphenazine and Amitriptyline Hydrochloride combinations - Triavil 2-10, Triavil 2-25, Triavil 4-10), Maprotiline (Ludiomil), Desipramine (Norpramin, Pertofrane), Trimipramine (Surmontil, Trimipramine Maleate), Imipramine (Imipramine Hydrochloride, Imipramine Pamoate, Janimine, Pramine, Presamine, Tofranil, Tofranil-pm), Protriptyline Hydrochloride (Vivactil), Agomelatine (Valdoxan), Reboxetine (Edronax, Vestra), Norvale (Mianserin,Bolvidon, Tolvan), Trazodone (Desyrel,
Trazodone Hydrochloride, Trialodine), Mirtazapine (Remeron, Remeron Soltab), Nefazodone (Nefazodone Hydrochloride, Serzone), Bupropion (Aplenzin, Bupropion Hydrochloride, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban).

**Non-pharmacological and complementary and alternative medicine (CAM) therapies:**
cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and other psychotherapies (behavior therapy, counseling, problem-solving therapy, psychodynamic therapy, bibliotherapy, guided self-help, distraction therapy), light therapy, exercise (any type cardiovascular or strengthening or stretching and including yoga, hydrotherapy), CAM including whole body systems (e.g., acupuncture), mind-body medicine (e.g., meditation), manipulative and body-based practices (e.g., massage), energy medicine (e.g., reiki), biologically based practices (dietary supplements and herbal products (e.g., amino acids, vitamins and minerals, Inositol, herbs, methyl-folate (Deplin), omega-3 fatty acids, SAMe)).

**Augmenters (no formal indication for use as an antidepressant):** Buspirone (Buspar), Gepirone (Ariza), Tandospirone (Sediel), Atypical Antipsychotics (Risperidone (Risperdal), Olanzapine (Zyprexa), Quetiapine (Seroquel), Aripiprazole (Abilify), Ziprasidone (Geodon)), Psychostimulants (Amphetamine (Adderall), Methylphenidate (Ritalin), Dopamine agonists (Bromocriptine (Parlodel), Cabergoline (Dostinex), Pergolide (Permax), Pramipexole (Mirapex), Ropinirole (Requip), Apomorphine (Apokyn), Rotigotine (Neupro), Other drugs (Lithium, Pindolol, Tryptophan), Anticonvulsants (Carbamazepine (Tegretol), Sodium Valproate, Lamotrigine (Lamictal)), Antiprogestational agents (Mifepristone (Mifeprax)), Sex Hormones (Androgens (e.g., Testosterone), Estrogens, Progesterone), Thyroid medications (triiodothyronine (T3), Amisulpride (Solian), Phenytoin (Dilantin, Phenytek), Modafinil (Provigil, Alertec, Modavigil, Modiodal, Modafinil, Carim, Armodafinil, Nuvigil), N-methyl-D aspartate (NMDA) NR2B subunit selective agonist CP-101606, mecamylamine hydrochloride (Inversine), Atomoxetine (Strattera)).

Studies that used electroconvulsive therapy, vagal nerve stimulation, or repetitive transcranial nerve stimulation as the intervention were excluded.

For KQ4, we evaluated CPGs that focus on guidelines at a national level or from key professional organizations published in English, but not limited to any country.

**Types of Comparators**

We identified and included studies with comparative intervention groups. From a design hierarchy perspective, comparative group designs provide stronger evidence for efficacy and effectiveness than noncomparative designs.

The interventions (either alone or in combination) may be compared with any of the following:

1. **Placebo**
2. Same SSRI dose but different MDD population (for example, mild vs. severe MDD)
3. Same SSRI of different dose or duration
4. Other SSRI
5. Other antidepressant (from a different drug class)
6. Nonpharmacological or CAM therapies as described above
7. Adjunct therapy: combination of an augmenter plus SSRI
8. Adjunct therapy: combination of nonpharmacological or CAM therapy plus SSRI
9. Adjunct therapy: combination of augmenter and nonpharmacological or CAM therapy
Types of Outcomes

Primary outcomes include the following:
1. Adequate Response: response to treatment is defined as a minimum of 50 percent change relative to baseline using a standardized instrument.3,62
2. Remission: remission is defined as being free or nearly free of symptoms. It is typically established by achieving a threshold score using a standardized instrument.
3. Partial and Nonresponse: partial response refers to a change in baseline score from 25 to 49 percent. Nonresponse is defined as less than 25 percent change relative to baseline. We recognize that some of the studies will vary in their definition and this will be noted when detail is provided within the original study.
4. Speed of Response.
5. Relapse: relapse is defined as a return of symptoms satisfying the full syndrome criteria for an episode which occurs following a period of remission but before recovery. Relapse is the point at which recurrent symptoms are severe enough that the clinician determines an intervention is warranted. Relapse is related but distinct from the term recurrence. Recurrence is defined as the return of the disease after its apparent cessation (symptoms return after a period of remission).

Secondary outcomes include the following:
1. Quality of life
2. Adherence
3. Return to work
4. Global change as measured by global assessment scales
5. External service utilization

Additional Eligibility Criteria

Study Design

Inclusions:
1. Experimental studies with comparator groups (randomized and quasirandomized trials)
2. Observational studies with comparator groups (retrospective and prospective cohort, case control, and interrupted time series with comparison group)
3. Letters with study data and abstracts

Exclusions:
1. All other study designs (e.g., case series, qualitative studies)
2. Editorials, commentaries, and notes

Language of Publication

Non-English language publications were excluded.

Contacting Authors for Additional Data

For studies that included populations that had failed to respond to antidepressants that included SSRIs, study authors were contacted via email requesting additional stratified outcome data. Studies where the authors did not respond or contact could not be established were excluded.
Timing

There are no restrictions on study eligibility with respect to a minimum treatment interval.

Settings

Studies that recruited patients from primary care, outpatient, and inpatient mental health settings were included. There were no exclusions for study setting.

Clinical Practice Guideline Selection

We defined CPG as “systematically developed statements about specific clinical problems intended to assist practitioners and patients in making decisions about appropriate health care.” We included full guidelines and consensus statements but we excluded algorithms with no background or description of the process by which the algorithm was developed.

Data Extraction

Relevant fields of information were extracted from individual studies by trained data extractors using standardized forms and a reference guide. Prior to performing the data extraction, a calibration exercise was undertaken using a convenience sample of five included studies. Key study elements were reviewed by a second person (study investigator) with respect to study outcomes, seminal population characteristics (past psychiatric history elements and definition of prior “treatment failure”), and characteristics of the intervention. Disagreements were resolved by consensus.

Extracted data included:

- Study characteristics: first author, country of research origin, study design, sample size, (e.g., sample size calculation, power estimate), clinical indications, and study duration or length of followup.
- Patient population: age, gender, racial composition, socioeconomic status (e.g., income, education), sleeping disturbances or levels, comorbidities (e.g., psychiatric and medical histories, use of CAM treatments concurrently or historically), definition of treatment failure, and severity and duration of the depressive disorder.
- Study interventions and comparators: type of intervention/comparator (e.g., pharmacological, nonpharmacological), dosage of intervention/comparator (e.g., type, dose, method of administration), frequency and treatment fidelity for psychotherapy related interventions, treatment duration (e.g., total duration of care), duration of followup, and characteristics of treatment providers.
- Outcomes: type of instrument or scale, primary or secondary outcome status, type of effect measure (e.g., endpoint or change score, measure of variance), definition of “adequate” treatment response, and type of statistical analysis (e.g., intention to treat).

Assessment of Methodological Quality of Individual Studies

We interpret methodological quality to include primarily elements of risk of bias related to the design and conduct of the study. In addition, we evaluated the presence of other key biases, such as the funding bias, and a specific form of selection bias related to “treatment failure” being determined prospectively.

We selected the Risk of Bias Tool by the Cochrane Collaboration to assess randomized controlled trials (RCTs). The tool contains 12 items that include evaluation of the domains of...
randomization, blinding, cointervention, and selective outcome reporting biases. Criteria for evaluation are standardized for these domains. Inconsistency amongst raters was minimized by providing adequate training and standardized instructions; disagreements were resolved by consensus. We had selected the Newcastle Ottawa Quality Assessment Tool to assess risk of bias for observational studies but no study of this design was eligible. Additionally, we evaluated studies for adequacy of collecting and reporting harms using the McHarm Tool. This tool has been specifically designed for adverse events and captures domains related to the classification of harms, method of collection (active versus passive), and also the level of withdrawals due to adverse events. We used the AGREE II to assess the methodological quality of the CPG. All tools can be viewed in Appendix B.

A study with low risk of bias was defined as a clinical trial fulfilling six or more of the 12 methodological quality criteria in the Risk of Bias Tool. A study with high risk of bias was defined as fulfilling fewer than six criteria. The classification of individual studies into categories of study limitations (high or low), were used to group studies for grading the strength of the evidence.

Applicability

We determined a priori the key attributes of applicability of our key research questions with respect to the population, intervention, comparator, and outcome in the context of a wider spectrum of patients (especially in primary care settings) that would likely benefit from these interventions in “real world” conditions.

Population characteristics to which these findings are applicable include:

- Men and woman older than 18 years of age and male and female adolescents aged 12 to 18 years
- People with a wide spectrum of previous episodes and variation in the course, including a first time episode of depression or several recurrences of MDD, dysthymia, or subsyndromal depression
- People with a complete spectrum of depression severity (mild to severe MDD and dysthymia)
- People with a wide spectrum of previous failures to SSRIs, from a first failed response for the current episode, to more than three failed responses to an SSRI for the current episode
- People with a wide spectrum of failed responses to previous antidepressant exposures for previous episodes of MDD, dysthymia, and subsyndromal depression

Population characteristics to whom the findings of this review are not applicable include:

- Adults or adolescents of either gender who have a primary diagnosis of bipolar disorder, schizophrenia, or major anxiety disorder

Intervention characteristics that these findings are applicable to include:

- For switches to new monotherapy treatment, antidepressant doses consistent with current recommended therapeutic dose ranges (as a minimum dose) applied for a minimum of 4 weeks,
- For combined therapy, there is variation in the doses for the added or augmenting agents; a clear trend for what ranges are applicable in this context.

The comparator treatments to which the research questions could ideally apply include those detailed in the comprehensive list of comparator treatments. Similarly, the outcomes selected for
this review would be applicable to those domains listed in the eligibility criteria; however, we would expect that these outcomes would be assessed using standardized instruments.

Data Synthesis

Qualitative Synthesis

For each trial, information on population characteristics (including history of treatment(s) for any previous episodes of depression, age of first diagnosis, etc.), study outcomes (both of benefit and of harm), sample sizes, settings, funding sources, treatments (type, dose, duration, and provider), methodological limitations, statistical analyses, and any important confounders is summarized in text and summary tables. We have stratified the presentation of results based on the type of depressive disorder (MDD, dysthymia, or subsyndromal depression) and by age (adolescent or adult).

Additionally, we grouped study results: (1) according to the index treatment categories (monotherapy or combined therapies) and the corresponding comparator treatment; (2) the specific grouping of the pharmacological treatment (SSRI, nonSSRI, augmenting agents); and (3) nonpharmacological treatment. Forest plots and summary tables were generated to display primary study outcomes of response and remission.

Summary tables were created for CPGs stratified by country of origin, where possible.

Quantitative Synthesis

The decision to pool individual study results was based on clinical judgment with regards to the comparability of study populations, treatments, and outcome measures. Specifically, methodological quality (high risk of bias vs. low risk of bias), clinical diversity (characteristics of the study population, gender, disease severity), treatment (pharmacological, nonpharmacological), intervention duration (2 weeks vs. 12 months), and outcome characteristics (different measuring scales) of individual studies were considered. The extent of heterogeneity was based on the clinical appropriateness of the populations and interventions.

After the final set of eligible studies were extracted, a decision was made to not undertake meta-analyses due to the clinical heterogeneity, predominately due to the different types of interventions and comparators. We presented data in forest plots to visually demonstrate comparative effects across the differing drug and nonpharmacological interventions but did not estimate summary effects. STATA (Version 10, StataCorp, College Station, Texas, United States) software was used to estimate the relative risks (RR) (using a random effects model) for the outcomes of response and remission.

Subgroup and Sensitivity Analysis

No meta-analyses were undertaken in this CER, as study populations, interventions, and comparators were not deemed sufficiently similar. However, we considered specific factors in the qualitative presentation of the review findings. Our search yielded only two eligible studies that did not include subjects with MDD, and, as such, the impact of the type of depressive disorder could not be explored. Primary studies and guidelines applicable to adults and adolescents were identified, and the results were presented stratified by these two age groups. Factors that had the potential to impact study outcomes or account for the clinical heterogeneity, such as gender, number of previous failures, method of determining treatment failure, dose and
duration characteristics of the intervention, and type of treatment provider were extracted and explored. We summarized these features within the clinical groupings of study interventions monotherapy versus monotherapy, monotherapy versus combined therapy, and combined therapies versus combined therapies. Methodological heterogeneity was also explored within each of these intervention groupings.

**Rating the Body of Evidence**

We assessed the overall strength of the evidence (SOE) across the literature using the rating approach as specified by the AHRQ. The SOE can be classified into four grades based on the AHRQ approach: high, moderate, low, or insufficient. Grading of the SOE is applied to individual outcomes, which in this CER are the primary outcomes of benefit (response and remission) and harm (suicidality, weight gain, and sexual dysfunction); partial and nonresponse was either omitted or poorly reported in most studies and as such was not included in the GRADE tables. A grading of “high” would reflect high confidence that the evidence shows the true effect, and that further research is very unlikely to change confidence in the estimate of the effect. A grading of “low” would reflect low confidence that the evidence shows the true effect, and that further research is likely to change confidence, or the magnitude in the estimate of the effect. A grading of “moderate” reflects a moderate level of confidence and that additional research may change confidence. A grading of “insufficient” reflects that the evidence is not available, or what evidence is available does not permit a conclusion of substance.

There are several factors that may decrease the overall grading of the SOE and these include: (1) study limitations (predominately risk of bias criteria) and the type of study design (experimental versus observational); (2) consistency of results (degree to which study results for an outcome are similar (variability across studies is easily explained, range of results is narrow); (3) directness of the evidence (assesses whether interventions can be linked directly to the health outcomes); and (4) precision (degree of certainty surrounding an effect estimate for a specific outcome). Additional factors that can be considered when evaluating the SOE can include: (1) dose response; (2) plausible confounding that would decrease the effect; (3) magnitude of the effect; and (4) publication bias and other factors related to relevance to intended populations.

The AHRQ approach to rating the SOE considers the link between the intervention and the outcomes with respect to the domain of directness. In the context of this CER, the links between intervention and the outcomes are all direct, thus, this domain does not assist in discriminating studies from each other. We have accounted for this by considering directness as per the GRADE approach, regarding directness to the population, intervention, and comparator treatments as part of other considerations affecting the SOE. All of these factors were considered when grading the SOE and the overall ratings are detailed in summary tables.

**Publication Bias**

Although our search strategy is comprehensive and includes a grey literature search including sources for unpublished trials, there is always the potential for publication bias. Publication bias is important to assess in reviews with the use of drugs, as there is evidence to suggest that industry sponsorship may lead to negative trials not being published, that reporting of adverse events are more favorable to the funder, and that there may be delay in publication of negative findings.

Our grey literature search was undertaken by the AHRQ Scientific Resource Centre research librarian. Part of this extensive search included a large number of citations from regulatory
databases, such as the FDA and clinical trial registries. These sources were searched to identify unpublished or ongoing trials in an attempt to minimize publication bias. Since there were less than 10 studies focusing on any single intervention, no funnel plots were produced, nor was a meta-analysis undertaken.
Results

Figure 2 shows the number of citations retrieved in the search from bibliographic and grey literature sources. From an initial 46,884 citations from the seven databases, 2,380 were duplicates. Following the initial screen of title and abstract by two reviewers, 36,031 studies were excluded, indicating that the citation was any of the following: (1) a commentary, editorial or narrative review, (2) not published in English; or, (3) not focused on the treatment of depression. At the next level of title and abstract screening, an additional 8,473 citations were excluded as they were: (1) not a primary study, systematic review, or guideline, (2) not a population with major depressive disorder (MDD), dysthymia, or subsyndromal depression; or, (3) evaluated only electroconvulsive therapy, transmagnetic stimulation, or vagal nerve stimulation as treatments for depression. A total of 3,147 citations were then screened at full text. Figure 2 details the reasons for exclusion at full text. An additional 1,682 citations were derived from grey literature sources and reviewed for relevancy. Systematic reviews published from 2005 forward were screened for potentially relevant citations that may not have been captured by the search. Forty-four primary studies (74 publications) were eligible for adults and adolescents. Twenty-seven guidelines in 33 publications were eligible.

Publications that presented subgroup analyses, secondary analyses, re-analyses, results of different outcomes (not a primary outcome measure), or results for different time points on the same study cohort were considered to be secondary records (or companion publications) to the original studies. For example, there are multiple analyses and publications related to a single study cohort from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. In this study, subjects were evaluated prospectively (level 1) for response to a selective serotonin reuptake inhibitor (SSRI), and those who did not respond were followed forward for seven new treatment arms (level 2). Those that failed level two treatments received additional treatments up to level five. STAR*D is included here as a single study with 15 eligible publications; an additional 44 publications based on the STAR*D cohort were excluded because they described results from level 1 only (the prospective evaluation of citalopram efficacy) or because they were overview summaries.

Full text screening identified 148 studies with an appropriate design, but for which only a proportion of the sample comprised subjects that were initially treated with an SSRI. In most studies, initial treatment consisted of a variety of possible antidepressants that included, but were not limited to, SSRI medications. The corresponding authors of these studies were contacted by email and asked to provide data stratified for the subgroup treated with an SSRI. Seven authors of 10 publications from 6 studies provided additional information specific to the SSRI failed subjects and these data are reported in this review. For the remaining 138 studies, 22 authors indicated that they could not provide SSRI failed subject results, 93 did not respond to email contact by the specified cut-off date, and for 23, contact information could not be found Appendix C provides a list of excluded studies and the reasons for their exclusion.

We present the review findings by Key Question (KQ) and further stratified by adults and adolescents.
Figure 2. Flow of studies to final number of eligible studies

Level 1
Title & Abstract
46,884
Excluded = 36,031
Duplicate = 2,380

Level 2
Title & Abstract
8,473
Excluded = 5,356

Level 3
Full Text
n=3,147
Excluded
n=2,782
Not an eligible study design................................. 692
Not an eligible population/diagnosis ....................... 40
Not an eligible population/treatment .................. 1,656
Not an eligible guideline/before 2004 .................. 59
Mixed antidepressants; some failed on SSRI ...... 138
STARD, an overview, level 1 data, other reason..... 51
Systematic Review before 2005 .......................... 146

Grey Literature
n=1,682
Excluded Grey Literature
n=1,682

Systematic Review 2005 forward
(Relevant topic, citations cross-matched)
n=261
Excluded Systematic Review 2005 forward
n=261

Primary Study
Adult = 41
Adolescent = 3
Companion = 33
n=74

Guideline Recommendation = 27
Companions = 6
n=33
KQ1. Among adults and adolescents with Major Depressive Disorder, Dysthymia, and Subsyndromal Depression who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

KQ1a. How does the efficacy/effectiveness vary among the different monotherapies and combined therapies?

Forty-four unique studies were eligible for KQ1. Forty-one studies (61 publications)\(^ {44,79,137,150}\) included adults and three studies (13 publications)\(^ {42,138-149}\) included adolescents. With respect to the studies that evaluated adults, there were five studies\(^ {107,150,178-180}\) for which results are not presented, and one for which on partial results are presented.\(^ {112}\) As well, seven of the STAR*D studies were not extracted: three studies\(^ {181-183}\) presented results for subjects after two or three additional treatment modifications following the first treatment failure (treatment levels three to five), three studies did not present data specific to any treatment,\(^ {184-186}\) and one study\(^ {187}\) presented cost outcomes based on modeling rather than actual cost data. Four studies did not have data extracted\(^ {178-180}\) or were only partially extracted,\(^ {112}\) as they included treatment protocols that evaluated prospective failure to subsequent nonSSRI or combination therapies prior to randomization to a new treatment (similar to level 3 and beyond in the STAR*D cohort), or participants were recruited because of previous failures including nonSSRI treatments.\(^ {180}\) The authors of these studies, and the authors from three STAR*D publications\(^ {181-183}\) were contacted and asked for results specific to the stream of patients that had failed an SSRI prior to the switch to the new intervention being tested; all authors responded and indicated that this information was not available. There were two additional studies\(^ {107,150}\) that were not extracted: these studies used withdrawal designs (maintenance trials), in which subjects who had successfully responded to the combination of an SSRI and an augmenting agent were then randomized to maintain the current treatment or to switch back to monotherapy.

Similarly, from the three eligible studies that evaluated adolescents, two studies (10 publications) had data that could be extracted.\(^ {42,138,140,141,144-149}\) One study\(^ {139,142,143}\) (3 publications) called the Treatment of Adolescents Study (TADS), indicated that some subjects in the pharmacological arm were evaluated beyond the first prospective failure to an SSRI (phase 2 and 3), but did not present these results. The author was contacted and there was confirmation that this information was not available.
Treatment in Adults Who Have Had Inadequate Response to an SSRI

Key Messages

When altering doses or switching to a different monotherapy in patients with inadequate response to an SSRI:

- There is low quality evidence to determine whether a switch to a non-SSRI antidepressant is different than a switch to another SSRI to affect response and remission.
- There is low quality evidence to determine if a switch to a non-pharmacological treatment is different than a switch to another antidepressant.
- There is low quality evidence that increasing the dose of an antidepressant is different to maintaining standard doses to affect response and remission.
- The majority of studies did not design their protocols to test superiority.

Augmenting therapies in patients with inadequate response to an SSRI:

- There is low quality evidence that response and remission rates following switch to a different antidepressant (monotherapy) are comparable to the addition of another treatment (combined therapy) in patients with inadequate response to treatment with an SSRI.
- There is low quality evidence that the addition of an atypical antipsychotic medication is different to the addition of a placebo in patients who have had an inadequate response to an SSRI.
- There is insufficient evidence that the addition of other augmenting agents is superior to the addition of a placebo in patients who have had an inadequate response to an SSRI.

Combined therapies in patients with inadequate response to an SSRI:

- There is insufficient evidence that any combined therapy was superior to any other to affect response and remission.

Studies to date include a restricted range of patients, with a preponderance of white women between the ages of 40 and 50 and a relatively large number of past depressive episodes.

There were 41 studies evaluating adults and all but two included subjects with MDD; one study evaluated subjects with subsyndromal depression, and one, subjects with dysthymia. As noted previously, five studies and seven STAR*D publications did not have data that could be extracted. Additionally, three STAR*D publications and two studies present results on predictors of failed response in the population of interest and these are presented in KQ4. We present the study results for the eligible and extracted studies based on the type of treatment comparisons as follows: (1) monotherapy compared with monotherapy; (2) monotherapy compared with combined therapy; and, (3) combined therapy compared with combined therapy. Some studies evaluated more than two treatment arms, and presented monotherapy compared with monotherapy results, as well as monotherapy compared with combined therapy. As such, some studies are included in multiple sections.
Monotherapy Treatment Compared With Monotherapy Treatment in MDD

Overview of Study PICOT\textsuperscript{a} Characteristics

There were twelve studies (18 publications)\textsuperscript{44,81,85,88,90,99,100,102-104,106,110-112,115,119,121,122} that compared monotherapy interventions in subjects who had failed to respond to an SSRI. Three studies\textsuperscript{85,90,119} evaluated a switch to another antidepressant. Five studies\textsuperscript{88,112,119,121,122} had three treatment arms for which two arms compared single interventions directly. The STAR*D study\textsuperscript{44,81,99,100,102,110,111} (labeled as level 2 subjects within this study), evaluated four monotherapy interventions and one treatment included cognitive behavioral therapy (CBT). One study (two publications)\textsuperscript{103,106} evaluated two methods of switching to the same anti-depressant. Two studies\textsuperscript{104,119} compared dose escalations of an SSRI. One study\textsuperscript{115} included subjects who failed to respond to SSRI and nonSSRI antidepressants and the author subsequently provided some results specific to the failed SSRI subgroup.

In total, there were 2,611 participants in treatment arms evaluating single interventions within these 12 studies. The sample size in these studies varied from 18\textsuperscript{122} to 789;\textsuperscript{44} the sample sizes per treatment arm varied from eight\textsuperscript{122} to 250.\textsuperscript{44} Six studies (9 publications)\textsuperscript{44,85,88,90,100,103,106,110,119} exceeded a total sample size of 101 and one study\textsuperscript{122} had less than 30 subjects. For one study\textsuperscript{115} that had a mixed sample of response failures, 58 of 77 subjects were from the SSRI failure subgroup.

Population

Women were the majority of subjects in all studies and female gender distributions varied from 60 to 69 percent\textsuperscript{44,81,85,88,90,99,100,102,104,110,111,119} to greater than 70 percent.\textsuperscript{103,106,121,122} One study\textsuperscript{112} reported gender characteristics for a larger sample (n=131) but not for the subgroup extracted for this review (n=41). Another study\textsuperscript{115} reported characteristics for a mixed sample (failure to respond to an SSRI and nonSSRI) and showed a larger proportion of women (approximately double). No studies reported either significant main effects of gender or significant interactions between gender and response rates across treatment groups.

The racial composition was predominately white race and varied from 60 percent,\textsuperscript{104} 80 percent,\textsuperscript{44,100,110,111} 90 percent,\textsuperscript{90} to 100 percent.\textsuperscript{103,106} Five studies did not report ethnicity.\textsuperscript{85,112,115,119,121} Although generally not evaluated, there were no differential patterns of response noted to be based on ethnicity.

Mean ages varied from 40 to 44 years in eight studies,\textsuperscript{44,85,88,90,104,112,119,122} 45 to 49 years in two studies (3 publications),\textsuperscript{103,106,121} and 54 years in another study.\textsuperscript{115}

Characteristics of the “Inadequate Response” for Enrollment

Table 1 shows the manner in which failure to respond to an SSRI was established in the reported studies. Four studies determined failure retrospectively and study subjects were on an SSRI at the time of entry into the trial.\textsuperscript{85,90,103,106,121} Where inadequate response to the SSRI was determined prospectively, fluoxetine,\textsuperscript{88,122} citalopram,\textsuperscript{44} paroxetine,\textsuperscript{104,112} and sertraline\textsuperscript{119} were

\textsuperscript{a}PICOT is an acronym encompassing the basic elements that must be considered in developing a research question: the patient population, intervention or interventions, comparators, outcomes, and timeframe under consideration.
the SSRIs for which failure was established. No study evaluated subjects specifically for failed response to escitalopram or fluvoxamine alone.

Two studies\textsuperscript{112,119} excluded subjects with a history of failure over a two week period to any intervention (antidepressant or augmenting agent) used in the current study. One study\textsuperscript{103,106} excluded subjects with a lack of response in the current episode to a serotonin–norepinephrine reuptake inhibitor (SNRI). This study evaluated two methods of switching from an SSRI to duloxetine (an SNRI). One study\textsuperscript{109} excluded patients who had previously taken venlafaxine, another study\textsuperscript{85} excluded subjects who had failed to respond to citalopram or venlafaxine and one study\textsuperscript{104} excluded subjects who had failed to respond to paroxetine.

**Table 1. Method of establishing failure to SSRI and intervention in studies comparing monotherapy strategies following SSRI non-response**

<table>
<thead>
<tr>
<th></th>
<th>Change Dose/Duration of Current SSRI</th>
<th>Switch to Other SSRI Medication</th>
<th>Switch to Non-SSRI Medication</th>
<th>Switch to Nonpharmacological Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Rush\textsuperscript{44}</td>
<td>Rush\textsuperscript{44}</td>
<td>Rush\textsuperscript{44}</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>Thase\textsuperscript{88}</td>
<td>Shelton\textsuperscript{122}</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Rhue\textsuperscript{104}</td>
<td></td>
<td>Bondolfi\textsuperscript{112}</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Licht\textsuperscript{119}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Retrospective Trials** |                                     |                                 |                               |                                         |
| Medical record/confirmation clinician |         | Thase\textsuperscript{90}      |                               |                                         |
| Patient Self Report     | Lexon-Smith\textsuperscript{85}   |                                 | Lexon-Smith\textsuperscript{85} |                                         |
| On specific medication at study entry |     | Ferreri\textsuperscript{121} (Fluoxetine) | Perahia\textsuperscript{103,106} (Any SSRI) |                                         |

SSRI = selective serotonin reuptake inhibitor

**Mental Health Histories of Study Participants**

Four studies, using the Hamilton Depression scale (HAMD) 17-item version, reported mean baseline scores that varied from 19 (SD 7.3),\textsuperscript{44} 21 to 23 (SD 3.3 to 3.9),\textsuperscript{103,106} and 24 to 28.\textsuperscript{104,121} One study\textsuperscript{119} reported median HAMD scores of 23 (range 18 to 37). Another study\textsuperscript{90} used the HAMD 21, and baseline scores varied from 22 to 23. One study\textsuperscript{122} reported only that the minimum severity for eligibility was a HAMD 21 item score of 20 or greater. Two studies\textsuperscript{85,88} reported Montgomery-Åsberg Depression Rating Scale (MADRS) mean score of 30 to 31. One study\textsuperscript{112} reported baseline scores for a larger sample (n=131) but not the subgroup of interest (n=41).

The number of previous depressive episodes varied from a median of one episode (range zero to eight),\textsuperscript{112} two episodes (range zero to 35),\textsuperscript{119} or seven to eight episodes (range 12 to 15) in the STAR*D cohort.\textsuperscript{44} One study reported that approximately 72 percent of the study subjects had had at least one previous episode of depression.\textsuperscript{103,106} Another study\textsuperscript{88} reported that 45 percent of the olanzapine group and 79 percent of the fluoxetine group of study subjects had had three or more lifetime episodes. One study\textsuperscript{85} had approximately 39 percent of subjects with no previous failures and 33 percent that had greater than 3 previous failures; another study had approximately 60 percent of subjects who had failed during their first episode of depression.\textsuperscript{104} Two studies\textsuperscript{90,122}
did not report the number of previous episode failures. A single study reported the proportion of subjects with recurrent depression as 75 percent.\textsuperscript{44} Two from four retrospective studies\textsuperscript{90,121} described how previous episode failures were defined; previous failures were defined as those that required treatment with antidepressants. None of the studies specified how information on previous episodes was captured (e.g., by patient report, medical record, etc.).

Length of the current episode was reported as a median value in three studies and a mean in four studies. Two studies indicated the proportion of subjects over various time intervals in weeks\textsuperscript{85} or months and years.\textsuperscript{104} One study did not report the mean length of the current episode.\textsuperscript{122} Median values for length of the current episode varied from eight weeks (range 2 to 52 weeks),\textsuperscript{112} and 16 to 20 weeks (range 0 to 960 weeks).\textsuperscript{119} Mean values varied from 28 to 32 weeks (range 0 to 42 weeks),\textsuperscript{105,106,121} 52 to 61 weeks (range 52 to 86 weeks),\textsuperscript{88,90} and 118 weeks (SD = 264 weeks).\textsuperscript{44} No study specified the manner for collecting the length of the current episode.

No study in this grouping reported baseline use of complementary and alternative medicines (CAM) at baseline or endpoint. One study excluded subjects who had used St. John's Wort within the preceding 14 days.\textsuperscript{90}

**Intervention and Comparators**

Ten studies were labeled as randomized controlled trials (RCT); however, the STAR*D cohort had a small proportion of subjects who accepted the randomized arm and as such we classify this as a controlled clinical trial (CCT). The number of treatment arms varied from two\textsuperscript{103,106} to four.\textsuperscript{44} Six studies had a prospective run in phase; the length of this phase varied between 4,\textsuperscript{112} 6,\textsuperscript{104,119,122} 8,\textsuperscript{88} and 12 weeks.\textsuperscript{44} Two studies included a washout period before switching to the new intervention; one study\textsuperscript{90} had an interval of 14 days (28 for fluoxetine) and another\textsuperscript{85} had an optional interval of 4 to 7 days placebo.\textsuperscript{90} Patient adherence was evaluated in only three studies; one study evaluated this as the number of pills consumed (varied from 94 to 97 percent adherence),\textsuperscript{88} another as not maintaining therapeutic drug monitoring (78 percent adherence),\textsuperscript{112} and one study evaluated pill counts and anamnesis.\textsuperscript{104}

Table 2 shows the comparison and treatment interventions for the studies evaluating monotherapy. The monotherapy included: (1) dose escalation with or without switching from an SSRI; (2) switch to another SSRI; (3) switch to an SNRI; (4) method of switching to an SNRI; (5) switch to an antidepressant; and (6) method of switching to an augmenting agent. There were three studies that evaluated dose escalations in sertraline (100mg/d and 200mg/d),\textsuperscript{119} paroxetine (20mg/d and 30 mg/d),\textsuperscript{104} and venlaxafine (mean dose 148mg/d and 309mg/d).\textsuperscript{90} Two of these dose comparison trials\textsuperscript{90,104} followed switches from another SSRI.

Two studies evaluated a switch to sertraline, which represented treatment with a different SSRI. One study\textsuperscript{44} switched from citalopram to sertraline and used a maximal dose of 200mg/d (titrated from 50mg/d), and one study\textsuperscript{119} compared two doses of sertraline (100mg/d and 200mg/d). Another study switched from a noncitalopram SSRI to citalopram.\textsuperscript{104}

Four studies (five publications)\textsuperscript{44,85,103,106,112} evaluated a switch to the SNRI venlaxafine, venlaxafine extended release, bupropion, or duloxetine. Doses for venlaxafine varied from 37.5 to 375mg per day (extended release).\textsuperscript{44,85,90,112}

Two different methods of switching from the current SSRI to the new medication, duloxetine, were evaluated in one study (two publications),\textsuperscript{103,106} and as such the dose of 60mg per day was the same for both treatment arms. One study\textsuperscript{44} evaluated the use of sustained release
bupropion at a maximal dose of 400mg per day (titrated from 150mg per day). This same study had treatment arms for venlaxafine and sertraline.

Two studies\textsuperscript{88,122} compared maintenance fluoxetine treatment to olanzapine monotherapy; the doses of fluoxetine were 50mg per day in one study\textsuperscript{88} to a range of 20 to 60mg per day in the second study.\textsuperscript{122} Olanzapine dosages ranged from 6 to 18mg per day in one study\textsuperscript{88} and 5 to 20mg per day in the second study.\textsuperscript{122} Another study\textsuperscript{121} evaluated mianserin at a dose of 60mg per day.

### Table 2. Monotherapy studies showing the comparison and treatment interventions

<table>
<thead>
<tr>
<th>Author</th>
<th>Monotherapy 1</th>
<th>Monotherapy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licht\textsuperscript{119} 2002</td>
<td>Sertraline</td>
<td>Sertraline (higher dose)</td>
</tr>
<tr>
<td>Ruhe\textsuperscript{104} 2009</td>
<td>Paroxetine</td>
<td>Paroxetine (higher dose)</td>
</tr>
<tr>
<td>Thase\textsuperscript{88} 2006</td>
<td>Venlaxafine</td>
<td>Venlaxafine (higher dose)</td>
</tr>
<tr>
<td>Perahia\textsuperscript{103,106} 2008, 2009</td>
<td>Any SSRI*</td>
<td>Duloxetine (method of taper)</td>
</tr>
<tr>
<td>Rush\textsuperscript{44} 2006</td>
<td>Venlaxafine</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Rush\textsuperscript{44} 2006</td>
<td>Sertraline</td>
<td>Venlaxafine</td>
</tr>
<tr>
<td>Bondolfi\textsuperscript{112} 2006</td>
<td>Paroxetine</td>
<td>Venlaxafine</td>
</tr>
<tr>
<td>Birkenhager\textsuperscript{115} 2004</td>
<td>Tranylcypromine</td>
<td>Phenelzine</td>
</tr>
<tr>
<td>Lenox-Smith\textsuperscript{85} 2008</td>
<td>Citalopram</td>
<td>Venlaxafine</td>
</tr>
</tbody>
</table>

**Switching and/or Changing Dose**

**Switch to non-SSRI Antidepressant**

**Switch to Augmenting Agent**

**Switch to Nonpharmacological Treatment**

CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitor

### Primary Outcomes

Three studies indicated that remission was the primary outcome, defined as a MADRS total score of less than 10,\textsuperscript{112} HAMD-17 score less than 7,\textsuperscript{88,104} or the Quick Inventory of Depressive Symptoms Self Report (QIDS-SR-16) score less than 5.\textsuperscript{44} Three studies indicated that the primary outcome was response based on a 50 percent reduction in the HAMD-17\textsuperscript{119} or HAMD-21.\textsuperscript{104,115} Five studies indicated that efficacy (as measured by a change in score and differences between groups) was the primary outcome, assessed using the HAMD-17,\textsuperscript{103,106} HAMD-21\textsuperscript{85,90} or MADRS scores.\textsuperscript{88,122} One study\textsuperscript{121} indicated that both response and remission as determined by the HAMD-17 were primary outcomes. All studies reported proportions of response (50 percent change relative to baseline) or remission (based on primary outcome threshold scores for specific instruments). Few studies evaluated outcomes other than response and remission (see efficacy section below).

### Timing of the Interventions

Table 3 details the run-in and treatment intervals for the studies comparing monotherapy treatments. The majority of studies evaluated response to the new treatment for six weeks or greater. Similarly, the majority of studies evaluated prospective failure for six weeks or greater.
Table 3. Length of the run-in and treatment phases for all studies

<table>
<thead>
<tr>
<th>Length of Treatment</th>
<th>2/3 Weeks</th>
<th>4/5 Weeks</th>
<th>6 Weeks</th>
<th>8 Weeks</th>
<th>&gt;8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective Failure Run-In Phase</td>
<td>Bondolfi(^{112})</td>
<td>Licht(^{119}) Shelton(^{122}) Ruhe(^{104})</td>
<td>Thase(^{88})</td>
<td>Trivedi(^{113}) Rush(^{110}) Thase(^{110})</td>
<td></td>
</tr>
<tr>
<td>Prospective Failure Treatment Phase</td>
<td>Bondolfi(^{112})</td>
<td>Licht(^{119})</td>
<td>Thase(^{88}) Ruhe(^{104})</td>
<td>Trivedi(^{113}) Rush(^{110}) Thase(^{110}) Shelton(^{122})</td>
<td></td>
</tr>
<tr>
<td>Retrospective Failure Studies</td>
<td>Birkenheger(^{115}) Ferreri(^{121})</td>
<td>Thase(^{90})</td>
<td>Perahia(^{103,106}) Lenox-Smith(^{85})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Setting

The studies comparing monotherapies were conducted in Europe (Spain, Italy, France, and the United Kingdom),\(^{103,106}\) Switzerland,\(^{112}\) Denmark and Iceland,\(^{119}\) France,\(^{121}\) the Netherlands,\(^{104,115}\) Australia,\(^{85}\) Canada,\(^{88}\) and the United States (three studies, nine publications).\(^{44,81,90,100,102,111,122}\)

Study participants were all recruited from outpatient psychiatric settings and outpatient primary care.\(^{44,90,104}\) Two studies recruited from both outpatient and inpatient psychiatric settings.\(^{85,121}\) One study recruited subjects from an inpatient setting.\(^{115}\)

Risk of Bias

Figure 3 shows the distribution of the evaluation for risk of bias using thirteen criteria. None of the seven studies clearly described the method of randomization. All studies were at low risk from biases associated with compliance to treatment, selective outcome reporting, showing reasons for dropouts, or for balancing of important prognostic factors at baseline. For the remaining criteria, only half the studies were at low risk of bias, particularly for randomization. In particular, the role of the funding agency was not specified in half the studies. All but two studies\(^{44,104}\) were funded by a pharmaceutical company with a financial interest in one of the drugs under investigation.

Three studies indicated that there was a washout period. One study\(^{90}\) included a 14 day (28 days for fluoxetine) washout period before randomization to new interventions; a second study\(^{85}\) allowed for an optional 4- or 7-day washout placebo. A third study\(^{115}\) had a one week washout from fluvoxamine. Lack of washout in the studies with olanzapine and fluoxetine\(^{88,122}\) may be problematic, as fluoxetine has a long half life (approximately 4 weeks) and the participants are therefore essentially on cotherpay for at least several weeks, even if they are only having olanzapine administered. Most SSRIs have a half life of no more than five days and any very early side effects from the new treatment could actually represent withdrawal from the SSRI, if in fact subjects were being switched. As a group, these monotherapy studies are considered to have moderate risk of bias given that half of the “risk of bias” items were not met or there was uncertainty.
Outcomes of Response and Remission

Overall, none of the therapeutic approaches (dose change with or without medication switch, or switch to different antidepressant, augmenting agent, or nonpharmacological therapy) showed any advantage over any other. Table 4 shows the rates of response and remission for all monotherapy comparisons, but there are some limitations in directly comparing response and remission rates due to varying definitions across studies. As noted previously, all but one study comparing various monotherapies defined “response” as a 50 percent change (improvement) relative to baseline for either the HAMD or MADRS; two studies had minor variations to this definition including: 1) 50 percent reduction and a score of 14 on the HAMD-17,115 and, 2) a 50 percent reduction on the HAMD or MADRS and CGI improvement (level 1 or 2).85 One study defined response as a reduction in the HAMD score equivalent to the “decrease pretreatment.”90 One study reported only response and remission rates for a subgroup of patients with a baseline score of greater than 31 on the HAMD-21 but not the total sample.85 Thresholds for remission for studies using the HAMD varied from seven to eight and for the MADRS less than eight or 10.

From the three studies evaluating dose changes, only one trial119 had confidence intervals that did not cross the midpoint, suggesting that the lower dose of 100mg of sertraline plus placebo
was superior to 200mg of sertraline plus placebo; response rates of 70 percent compared to 54 percent and remission rates of 38 and 28 percent respectively were reported (Table 4).

In the studies that switched to other antidepressants, none were shown to confer any relative advantage in response and remission rates. As part of the STAR*D trial, few differences were shown for the outcomes of response or remission when patients were switched from citalopram to either another SSRI (sertraline) or a nonSSRI (bupropion or venlafaxine). Similarly, in this same trial, patients who were switched to another monotherapy medication (subgroup) had comparable rates of response to those that were switched to CBT alone.

Figure 4 depicts the rates of response for studies comparing monotherapy treatments. Figure 5 depicts the rates of remission for studies comparing monotherapy treatments.

Other Outcomes

Three studies evaluated speed of response. The STAR*D showed no statistically significant differences for monotherapy treatments with respect to speed of response or remission. A second study showed no statistically significant differences between the monotherapy arms with respect to speed of response. The third study found no statistical differences between groups with differing doses of venlafaxine.

Only 4 of 12 studies evaluated quality of life outcomes and all studies showed no statistically significant differences in any of these measures between treatment arms. One study compared Visual Analogue Scale scores for pain (overall and various body parts); although there were no statistical differences between the two methods of switching to duloxetine, there were statistically significant decreases on the Visual Analogue Scale for pain, SF36-bodily pain scale, and the symptom questionnaire somatic scale.
Figure 4. Forest plot of monotherapy versus monotherapy interventions for the outcome of response

Study | Risk ratio (95% CI) | No. of events | Risk ratio | No. of events |
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Licht 2002&lt;sup&gt;17&lt;/sup&gt; (SER1+PBO vs. SER2+PBO, H)</td>
<td>0.79 (0.63, 0.99)</td>
<td>54/98</td>
<td>0.001</td>
<td>80</td>
</tr>
<tr>
<td>Ruhe 2009&lt;sup&gt;18&lt;/sup&gt; (PAX2 vs. PAX3, H-17)</td>
<td>0.90 (0.44, 1.82)</td>
<td>10/30</td>
<td>0.001</td>
<td>80</td>
</tr>
<tr>
<td>Thase 2006&lt;sup&gt;19&lt;/sup&gt; (VEN1 vs. VEN3, H-21)</td>
<td>1.23 (0.91, 1.66)</td>
<td>53/109</td>
<td>0.001</td>
<td>80</td>
</tr>
</tbody>
</table>

Switch Antidepressant

Bondolfi 2006<sup>20</sup> (PAX vs. VEN, M) | 0.40 (0.02, 7.57) | 0/9 | 0.001 | 80 |
*Rush 2006<sup>21</sup> (SER vs. VEN, Q-16) | 1.06 (0.79, 1.41) | 70/250 | 0.001 | 80 |
*Rush 2006<sup>21</sup> (SER vs. BUP, Q-16) | 0.98 (0.73, 1.32) | 62/239 | 0.001 | 80 |
*Rush 2006<sup>21</sup> (VEN vs. BUP, Q-16) | 0.93 (0.69, 1.24) | 62/239 | 0.001 | 80 |
Perahia 2008<sup>22</sup> (DS DLX vs. TS DLX, H) | 1.09 (0.91, 1.30) | 109/185 | 0.001 | 80 |
Birkenhager 2004<sup>23</sup> (TCP vs. PLZ, H) | 1.25 (0.70, 2.22) | 14/28 | 0.001 | 80 |

Switch and/or Add Augmenting Agent

Thase 2007<sup>24</sup> (FLX vs. OLZ, M) | 0.88 (0.64, 1.20) | 5/197 | 0.001 | 80 |
Shelton 2001<sup>25</sup> (FLX+PBO vs. OLZ+PBO, M) | 0.27 (0.01, 5.92) | 0/10 | 0.001 | 80 |
Ferreri 2001<sup>26</sup> (FLX+PBO vs. MIN+PBO, M) | 1.28 (0.74, 2.21) | 16/34 | 0.001 | 80 |

Switch and/or Add Non-Pharmacological

*Rush 2006<sup>21</sup>/Thase 2007<sup>27,28</sup> (SER vs. CBT, Q-16) | 0.84 (0.44, 1.60) | 8/36 | 0.001 | 80 |
*Rush 2006<sup>21</sup>/Thase 2007<sup>27,28</sup> (VEN vs. CBT, Q-16) | 0.79 (0.42, 1.51) | 8/36 | 0.001 | 80 |
*Rush 2006<sup>21</sup>/Thase 2007<sup>27,28</sup> (BUP vs. CBT, Q-16) | 0.86 (0.45, 1.64) | 8/36 | 0.001 | 80 |
*Rush 2006<sup>21</sup>/Thase 2007<sup>27,28</sup> (Med vs. CBT, Q-16) | 0.83 (0.41, 1.68) | 8/36 | 0.001 | 80 |

BUP = bupropion; BUS = buspirone; CBT = cognitive behavioral therapy; DS DLX = direct switch duloxetine; FLX = fluoxetine; H = Hamilton Depression Rating Scale; H-17 = Hamilton Depression Rating Scale – 17 item; H-21 = Hamilton Depression Rating Scale – 21 item; M = Montgomery-Asberg Depression Rating Scale (MADRS); MIN = mianserin; Med = medication; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PLZ = phenelzine; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; STS DLX = start-taper switch duloxetine; TCP = tranylcypromine; VEN = venlafaxine

*Represent STAR*D studies.

Note: Lenox-Smith 2006<sup>29</sup> did not provide data for the entire sample and is not included in this figure.
Figure 5. Forest plot of monotherapy versus monotherapy interventions for the outcome of remission

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>No. of Monotherapy 1</th>
<th>Monotherapy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switch and/or Change Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licht 2002 (SER+PBO vs. SER2+PBO, H)</td>
<td>0.76 (0.51, 1.14)</td>
<td>28/9</td>
<td>37/99</td>
</tr>
<tr>
<td>Ruhe 2009 (PAK2 vs. PAK3, H-17)</td>
<td>1.80 (0.36, 9.06)</td>
<td>4/30</td>
<td>2/27</td>
</tr>
<tr>
<td>Thase 2008 (VEN1 vs. VEN3, H-21)</td>
<td>1.24 (0.75, 2.04)</td>
<td>26/109</td>
<td>22/114</td>
</tr>
<tr>
<td>Switch to New Antidepressant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Rush 2006 (SER vs. VEN, H-17)</td>
<td>1.41 (0.99, 1.99)</td>
<td>62/25</td>
<td>42/238</td>
</tr>
<tr>
<td>*Rush 2006 (SER vs. VEN, Q-16)</td>
<td>0.94 (0.69, 1.27)</td>
<td>62/25</td>
<td>63/238</td>
</tr>
<tr>
<td>*Rush 2006 (SER vs. BUP, H-17)</td>
<td>1.21 (0.84, 1.75)</td>
<td>51/23</td>
<td>42/238</td>
</tr>
<tr>
<td>*Rush 2006 (VEN vs. BUP, H-17)</td>
<td>1.01 (0.75, 1.36)</td>
<td>64/23</td>
<td>63/238</td>
</tr>
<tr>
<td>*Rush 2006 (VEN vs. BUP, Q-16)</td>
<td>0.86 (0.62, 1.19)</td>
<td>51/23</td>
<td>62/250</td>
</tr>
<tr>
<td>Perahia 2008 (DS DLX vs. TS DLX, H)</td>
<td>1.03 (0.76, 1.40)</td>
<td>61/23</td>
<td>62/250</td>
</tr>
<tr>
<td>Birkenhager 2004 (TCP vs. PLZ, H)</td>
<td>0.36 (0.08, 1.63)</td>
<td>2/28</td>
<td></td>
</tr>
<tr>
<td>Switch to Augmenting Agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase 2007 (FLX vs. OLZ, M)</td>
<td>0.88 (0.56, 1.39)</td>
<td>29/197</td>
<td>34/203</td>
</tr>
<tr>
<td>Ferreri 2001 (FLX+PBO vs. MIN+PBO, M)</td>
<td>1.81 (0.80, 4.08)</td>
<td>12/36</td>
<td>7/38</td>
</tr>
<tr>
<td>Switch to Non-Pharmacological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (SER vs. CBT, H-17)</td>
<td>0.94 (0.52, 1.73)</td>
<td>9/36</td>
<td>63/238</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (VEN vs. CBT, H-17)</td>
<td>1.01 (0.55, 1.85)</td>
<td>9/36</td>
<td>62/250</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (BUP vs. CBT, H-17)</td>
<td>0.96 (0.53, 1.76)</td>
<td>9/36</td>
<td>62/239</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (MME vs. CBT, H-17)</td>
<td>0.90 (0.46, 1.73)</td>
<td>9/36</td>
<td>24/86</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (SER vs. CBT, Q-16)</td>
<td>1.15 (0.68, 1.97)</td>
<td>11/3</td>
<td>63/238</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (VEN vs. CBT, Q-16)</td>
<td>1.23 (0.72, 2.11)</td>
<td>11/3</td>
<td>62/250</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (BUP vs. CBT, Q-16)</td>
<td>1.20 (0.70, 2.05)</td>
<td>11/3</td>
<td>61/239</td>
</tr>
<tr>
<td>*Rush 2006/Thase 2007 (Med vs. CBT, Q-16)</td>
<td>1.14 (0.62, 2.09)</td>
<td>11/3</td>
<td>23/86</td>
</tr>
</tbody>
</table>

BUP = bupropion; CBT = cognitive behavioral therapy; DS DLX = direct switch duloxetine; FLX = fluoxetine; H = Hamilton Depression Rating Scale; H-17 = Hamilton Depression Rating Scale – 17 item; H-21 = Hamilton Depression Rating Scale – 21 item; M = Montgomery-Asberg Depression Rating Scale (MADRS); MIN = mianserin; Med = medication; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PLZ = phenelzine; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; TCP = tranylcypromine; STS DLX = start-taper switch duloxetine; VEN = venlafaxine

*Represent STAR*D studies.
Table 4. Summary of reported rates of response and remission for studies comparing monotherapy treatment to other monotherapy treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response a n (%)</th>
<th>p Value</th>
<th>Remission b n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch and/or Change Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licht 2002</td>
<td>6</td>
<td>HAMD-NS</td>
<td>99</td>
<td>SER 100 mg/d</td>
<td>69 (70)</td>
<td>0.03</td>
<td>37 (38)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>SER 200 mg/d</td>
<td>54 (64)</td>
<td></td>
<td>28 (29)</td>
<td></td>
</tr>
<tr>
<td>Ruhe 2008</td>
<td>6</td>
<td>HAMD-17</td>
<td>30</td>
<td>PAX 20</td>
<td>10 (37.0)</td>
<td>0.788</td>
<td>2 (7.4)</td>
<td>0.673</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>PAX 30-50</td>
<td>10 (33.3)</td>
<td></td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Thase 2008</td>
<td>8</td>
<td>HAMD-21</td>
<td>119</td>
<td>VEN-ER 148 mg/d</td>
<td>45 (39.0)</td>
<td>NS</td>
<td>22 (19.0)</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>113</td>
<td>VEN-ER 309 mg/d</td>
<td>53 (49.0)</td>
<td></td>
<td>26 (24.0)</td>
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<tr>
<td><strong>Switch to NonSSRI</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birkenhager 2004</td>
<td>5</td>
<td>HAMD-NS</td>
<td>30</td>
<td>TCP 61 mg/d</td>
<td>12 (40.0)</td>
<td>NT</td>
<td>6 (20.0)</td>
<td>NT</td>
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<td></td>
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<td>28</td>
<td>PLZ 79 mg/d</td>
<td>14 (50.0)</td>
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<td>2 (7.1)</td>
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<td>Bondolfi 2006</td>
<td>4</td>
<td>MARDS</td>
<td>19</td>
<td>PAX 40 mg/d</td>
<td>2 (10.5)</td>
<td>3 (15.7)</td>
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<td></td>
<td>9</td>
<td>VEN 150 mg/d</td>
<td>0 (0)</td>
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<td>0 (0)</td>
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<tr>
<td>Lenox-Smith 2006</td>
<td>12</td>
<td>HAMD-21</td>
<td>200</td>
<td>VEN-ER 75-300 mg/d</td>
<td>NR</td>
<td>0.953</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>206</td>
<td>CIT 20-60 mg/d</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Rush 2006</td>
<td>12</td>
<td>HAMD-17</td>
<td>238</td>
<td>SER 50-200 mg/d</td>
<td>63 (26.7)</td>
<td>NS</td>
<td>42 (17.6)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>VEN 37.5-375 mg/d</td>
<td>70 (28.2)</td>
<td></td>
<td>63 (26.4)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>239</td>
<td>BUP 150-400 mg/d</td>
<td>62 (26.1)</td>
<td></td>
<td>62 (24.8)</td>
<td></td>
</tr>
<tr>
<td>Perahia 2008, 2009</td>
<td>10</td>
<td>HAMD-17</td>
<td>183</td>
<td>direct switch DLX 60-120 mg/d</td>
<td>99 (54.4)</td>
<td></td>
<td>42 (17.6)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>185</td>
<td>start-taper switch DLX 60-120 mg/d</td>
<td>109 (59.6)</td>
<td></td>
<td>63 (26.4)</td>
<td></td>
</tr>
</tbody>
</table>

* = difference from baseline; ^ = difference from placebo
Table 4. Summary of reported rates of response and remission for studies comparing monotherapy treatment to other monotherapy treatments (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response n (%)</th>
<th>p value</th>
<th>Remission n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add Augmenting Agent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Thase^88 2007</td>
<td>8</td>
<td>MADRS</td>
<td>203</td>
<td>FLX 50mg/d</td>
<td>NR</td>
<td>NR</td>
<td>34 (16.7)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>197</td>
<td>OLZ 6-18mg/d</td>
<td>NR</td>
<td></td>
<td>29 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Shelton^122</td>
<td>8</td>
<td>MADRS</td>
<td>8</td>
<td>FLX 20-60mg/d</td>
<td>1 (10.0)</td>
<td>0.11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>OLZ 5-20mg/d</td>
<td>0 (0.0)</td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ferreri^121</td>
<td>6</td>
<td>HADRS 17</td>
<td>38</td>
<td>FLX 20mg/d</td>
<td>14 (37.0)</td>
<td>0.1</td>
<td>7 (18.5)</td>
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<td>34</td>
<td>MIN 60mg/d</td>
<td>16 (48.5)</td>
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<td>12 (35.2)</td>
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<td><strong>Add Non-Pharmacological</strong></td>
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<tr>
<td>Trivedi^113</td>
<td>12</td>
<td>HAMD-17</td>
<td>238</td>
<td>SER 50-200mg/d</td>
<td>63 (26.7)⁶</td>
<td>NS</td>
<td>42 (17.6)</td>
<td>NS</td>
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<tr>
<td>Thase^110</td>
<td></td>
<td>QIDS-SR16</td>
<td>250</td>
<td>VEN 37.5-375mg/d</td>
<td>70 (28.2)⁵</td>
<td>NS</td>
<td>62 (24.8)</td>
<td>NS</td>
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<td>239</td>
<td>BUP 150-400mg/d</td>
<td>62 (26.1)⁶</td>
<td>NS</td>
<td>51 (21.3)</td>
<td>NS</td>
</tr>
<tr>
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<td></td>
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<td>36</td>
<td>CBT</td>
<td>8 (22.2)*</td>
<td>NS</td>
<td>9 (25.0)</td>
<td>NS</td>
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<td>86</td>
<td>Medication</td>
<td>23 (26.7)</td>
<td>NS</td>
<td>24 (27.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; DLX = duloxetine; FLX = fluoxetine; HAMD = Hamilton Depression Rating Scale; HAMD-NS = Hamilton Depression Rating Scale not specified; MADRS = Montgomery-Åsberg Depression Rating Scale; MIN = mianserin; NR = not reported; NS = not significant; NT = not tested; OLZ = olanzapine; PAX = paroxetine; PLZ = phenelzine; QIDS-SR16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; SSRI = selective serotonin reuptake inhibitors; TCP = tranylcypromine; VEN = venlafaxine; VEN-ER = venlafaxine extended release

*Response was defined as 50 percent change relative to baseline for the rating scale specified, unless noted within the table.

^Remission was defined relative to the standard threshold value for the rating scale specified, unless noted within the table.

The QIDS-SR reported outcomes.

⑥A reduction in the HAMD score equivalent to the “decrease pretreatment”.^90

⑦50 percent reduction and a score of 14 on the HAMD-17.¹¹⁵

⑧50 percent reduction on the HAMD or MADRS and CGI improvement (level 1 or 2).³⁵
Monotherapy Versus Combined Therapy Interventions in MDD

There were 33 unique studies that evaluated monotherapy versus combined therapies. Two studies were withdrawal studies and were not extracted. From the remaining 31 studies, five evaluated nonpharmacological interventions combined with SSRI use. For level 2 subjects, the STAR*D study evaluated four monotherapy interventions and three combined therapies; the CBT monotherapy and citalopram with CBT arms were compared with pharmacological therapies combined, and the results are presented in the nonpharmacological section below. A single study evaluated two doses of an SSRI and the same SSRI in combination with an augmenting agent. There were six studies that had subjects who failed to respond to SSRI and non-SSRI antidepressants and subsequently provided some results specific to the failed SSRI group. The majority of studies compared the use of a single antidepressant to a combined therapy, which included an antidepressant with augmenting agents.

In total there were 4,537 participants in studies comparing monotherapy to combined therapies. The total sample size in these studies varied from 9 to 1,439; the sample sizes per treatment arm varied from 4 subjects to 307. Thirteen studies exceeded a total sample size of 101 and 9 studies had fewer than 30 subjects.

Overview of Study PICOT Characteristics

Population

There were two studies that predominately evaluated a single gender. One study evaluated men, as the intervention was testosterone used as the augmenting agent. Another study evaluated only women being treated with antidepressants alone or combined with exercise. The proportion of women in the other studies varied from greater than 70 percent in 13 studies, from 61 to 69 percent in 5 studies, from 51 to 59 percent in 2 studies, and from 45 to 49 percent in 2 studies. One study reported gender characteristics for a larger sample (n=131) but not for the subgroup (step 3A to 3C) extracted for this review (n=41).

There were seven studies for which the authors provided some stratified results specific to the subgroup that had failed to adequately respond to an SSRI. However, demographic data were not provided or available. As such, we have assumed that the SSRI failure subgroup are comparable to the whole sample within the study, as they represented over 50 percent of the total sample. When considering the proportion of the study samples who failed to respond adequately to SSRI treatment, there were two studies where the sample was 55 to 59 percent, 60 to 69 percent in two studies, and greater than 70 percent in three studies. In these seven studies, females represented the majority of the subjects in the following proportions; 1) greater than 80 percent in two studies, 2) from 70 to 79 percent in three studies, and 3) from 51 to 60 percent in two studies.

In the majority of studies, the proportion of men and women per treatment arm were similar with the exception of one small study with 20 subjects, which showed differences between groups greater than 10 percent. Information on racial composition or ethnicity was not reported.
in 18 studies. For the remaining studies, the majority of subjects were of the white race comprising between 75 to 89 percent of the sample in six studies and greater than 90 percent in seven studies. Mean age for the total samples varied from 40 to 44 years in 11 studies, 45 to 49 years in 13 studies, and greater than 60 years in 2 studies. One study did not report age characteristics of the very small sample (n=9). Two studies reported an age range of 21 to 54, and from 40 to 60 years.

### Inadequate Response

Table 5 shows the manner in which failure to an SSRI had been established. Fifteen studies determined failure prospectively in an open label manner. For the majority of these, the subjects were currently on the same antidepressant to which they had shown a poor response. Fourteen studies determined inadequacy of response retrospectively. For studies where inadequate response was determined prospectively, the SSRI to which failure was established included three studies each for fluoxetine, and sertraline, and two each for citalopram, escitalopram, and paroxetine. Six studies used any combination of SSRIs; three studies specified that fluvoxamine was not one of the SSRI evaluated and these same studies also included escitalopram. No studies evaluated subjects specifically for failed response to fluvoxamine alone.

There were nine studies that excluded subjects because of past failures to specific interventions. Five studies excluded subjects who reported two, three, or more previous failures. Three studies excluded subjects with a history of failure over a two week period or in the recent episode to any intervention (antidepressant or augmenting agent) used in the current study. Three studies excluded subjects who had an inadequate response to nonpharmacological interventions of electroconvulsive therapy (ECT) alone or with repetitive transcranial magnetic stimulation (rTMS) and vagal nerve stimulation (VNS) in a previous episode. The remaining 20 studies did not exclude or include subjects based on previous failures to any specific treatment.
Table 5. Method of establishing failure to SSRIs in studies comparing monotherapy to combination therapies

<table>
<thead>
<tr>
<th></th>
<th>MONOTHERAPY</th>
<th>COMBINED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Determining Inadequate Response</td>
<td>Dose or Duration Change</td>
</tr>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Rush(^{44})*</td>
<td>Rush(^{44})*</td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
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<tr>
<td>Fluoxetine</td>
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<td>Fluvoxamine</td>
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<td>Paroxetine</td>
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<td>Sertraline</td>
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<tr>
<td>Any SSRI</td>
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<tr>
<td><strong>Retrospective</strong></td>
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<tr>
<td>Medical chart</td>
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<tr>
<td>Self report</td>
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<td></td>
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<tr>
<td>Currently on SSRI or other antidepressant</td>
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</table>

AD = antidepressant; SSRI = selective serotonin reuptake inhibitors

*STAR*\(^{R}\)D publications.
Table 6 shows the baseline severity reported for the different studies. As expected the baseline scores tended towards the latter quarter of the maximum instrument scores, which suggests that subjects had symptoms consistent with those with moderate to severe depression. Two studies did not provide baseline scores.\textsuperscript{80,112} The number of previous depressive episodes varied from a median of one episode (range zero to 8),\textsuperscript{112} median of two (range zero to 35);\textsuperscript{119} or median of seven to eight (range 12 to 15) in the STAR*D cohort.\textsuperscript{44,110,113} The reported mean number of episodes varied from one to two previous episodes,\textsuperscript{93,94} and three to six.\textsuperscript{95,105,123,124,126,131} Another study\textsuperscript{88} reported that 45 percent of the olanzapine group and 79 percent of the fluoxetine group of study subjects had three or more lifetime episodes. Twenty-one studies did not report the number of previous failed episodes.\textsuperscript{79,80,82-84,86,87,89,91,92,96-98,101,108,109,114,118,120,122,126-128,130,132-135,137}

Two studies (three publications)\textsuperscript{79,109,126} reported the number of prior adequate antidepressant trials for the current episode and this varied from one adequate trial (67 percent) to three adequate trials (eight percent). Two studies\textsuperscript{95,124} showed some differences between treatment groups with respect to previous episodes, with the risperidone group having fewer previous failures. How previous episodes were defined and captured was not apparent in the majority of studies. No study in this grouping reported use of CAM at baseline or endpoint.

### Table 6. Distribution of baseline scores for primary outcomes as a proxy for severity of MDD

<table>
<thead>
<tr>
<th>Disease Specific Scale</th>
<th>Baseline Scores</th>
<th>Authors</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>Trivedi\textsuperscript{113}</td>
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<td>Rush\textsuperscript{44}</td>
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<td>Thase\textsuperscript{110}</td>
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Table 6. Distribution of baseline scores for primary outcomes as a proxy for severity of MDD (continued)

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<th>Disease Specific Scale</th>
<th>Baseline Scores</th>
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<tr>
<td>QIDS-SR16</td>
<td>Trivedi¹¹³</td>
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<tr>
<td>Other</td>
<td>Carta ¹²⁷</td>
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</tbody>
</table>

BDI = Beck Depression Inventory; HAMD = Hamilton Depression Rating Scale; HAMD-NS = Hamilton Depression Rating Scale not specified; MADRS = Montgomery-Åsberg Depression Rating Scale; QIDS-SR16 = Quick Inventory of Depressive Symptoms Self Report (16)

*Baseline scores were not provided but subjects must have had a score of 21 or greater for entry to the study.

Note that two studies⁸⁰,¹¹² did not provide baseline scores and some studies provided scores for more than one instrument.

**Intervention and Comparator**

All but three studies⁴⁴,¹¹⁰,¹¹³ employed an RCT design with at least some level of blinding. There were five studies⁹⁴,¹¹⁰,¹²⁷,¹³³,¹³⁵,¹³⁷ that evaluated the use of nonpharmacological interventions including CBT,⁹⁴,¹¹⁰ dialectical behavior therapy (DBT),¹²⁸ interpersonal therapy (IPT)¹³³,¹³⁵,¹³⁷ and exercise.¹²⁷ The remaining studies used pharmacological agents combined predominately with augmenting agents and a new SSRI or other antidepressants.

Table 7 shows that approximately one quarter of the studies had prospective run-in phases and treatment phases that exceeded 8 weeks. Two of the retrospective failure studies provided treatment for this same interval. One study evaluated the Step 3 of the treatment algorithm after only 2 weeks of treatment switch.

Table 7. Details the length of the run-in and treatment phases for all studies

<table>
<thead>
<tr>
<th>Length of Treatment</th>
<th>2/3 Weeks</th>
<th>4/5 Weeks</th>
<th>6 Weeks</th>
<th>8 Weeks</th>
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*Indicates treatment was 5 days.
Table 8 shows the combined interventions and all other treatment comparisons. Two studies included one treatment arm that evaluated an increased dose of sertraline\textsuperscript{119} or the addition of intravenous citalopram.\textsuperscript{82,83} Four studies had one treatment arm that evaluated a combination therapy that included the nonSSRI antidepressants clomipramine,\textsuperscript{82,83} bupropion,\textsuperscript{113} and desipramine.\textsuperscript{98,118}

The majority of studies evaluated combination therapies that included augmenting agents (26 from 33 studies). From studies with at least one treatment arm using a combination therapy that included an augmenting agent, there were five drugs or classes of drugs for which there was more than one study, and these included atypical antipsychotics (reserpodine, olanzapine, aripiprazole, quetiapine), lithium, buspirone, mianserin, and pindolol. There were four studies\textsuperscript{98,112,118,124} with at least one treatment arm evaluating the effect of adding lithium; doses varied from 600mg/d,\textsuperscript{98,118} to 800mg/d,\textsuperscript{124} and one study did not report the dose.\textsuperscript{112} There were five studies evaluating atypical antipsychotics,\textsuperscript{88,95,108,122,134} the doses were similar for studies evaluating olanzapine at 5-6mg/d,\textsuperscript{88,122} but varied from 0.5mg/d\textsuperscript{95} to 1mg/d in studies assessing risperidone.\textsuperscript{108} There were three studies (seven publications)\textsuperscript{44,92,97,110,115,120,130} evaluating buspirone employing final doses that varied from 47mg/d\textsuperscript{97} to 60mg/d.\textsuperscript{113} Two studies evaluated the use of mianserin\textsuperscript{119,121} with doses of 30mg/d\textsuperscript{119} and 60mg/d.\textsuperscript{121} The augmenting agent pindolol was also evaluated in two studies; the dose was not reported in one study\textsuperscript{93} and was 7.5mg/d in the second study.\textsuperscript{96}

**Table 8. Monotherapy versus combined therapy studies showing the comparison and treatment interventions grouped by type of intervention**

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
</table>
| Licht,\textsuperscript{119} 2002 | Sertraline + Placebo  
Sertraline (higher dose) + Placebo | Sertraline + Mianserin |
| Altamura,\textsuperscript{82,83} 2008 | SSRI + Placebo (saline) | SSRI + Citalopram (intravenous) |

**Add nonSSRI Antidepressant**

| Altamura,\textsuperscript{82,83} 2008 | SSRI + Placebo (saline) | SSRI + Clomipramine (intravenous) |
| Trivedi,\textsuperscript{113} 2006  
Rush,\textsuperscript{44} 2006  
Thase,\textsuperscript{110} 2007 | Switching to new monotherapy  
(Bupropion/Venlaxine/Sertraline/CBT) | Citalopram + Buproprion |
| Fava,\textsuperscript{118} 2002 | Fluoxetine + Placebo | Fluoxetine + Desipramine  
*Fluoxetine + Lithium* |
| Fava,\textsuperscript{98} 1994 | Fluoxetine | Fluoxetine + Desipramine  
*Fluoxetine + Lithium* |

**Add Augmenting Agent**

| Preskorn,\textsuperscript{80} 2008 | Paroxetine + Placebo | Paroxetine + CP-101606 |
| George,\textsuperscript{84} 2008 | Current SSRI + Placebo | Current SSRI + Mecamylamine  
Hydrochloride |
| Michelson,\textsuperscript{87,101,132} 2007 | Sertraline + Placebo | Sertraline + Atomoxetine |
| Shapira,\textsuperscript{89} 2006 | SSRI (Fluoxetine/Fluvoxamine/Paroxetine)  
+ Placebo | Current SSRI + Phenytoin |
| Seidman,\textsuperscript{91} 2005 | SSRI + Placebo injection | Current SSRI + Testosterone injection |
Table 8. Monotherapy versus combined therapy studies showing the comparison and treatment interventions grouped by type of intervention (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berman,109, 2007 Marcus,105,131 2008 Thase,126, 2007</td>
<td>Switched to new SSRI Escitalopram/Fluoxetine/Sertraline/Venlafaxine + Placebo</td>
<td>Switched to new SSRI (Escitalopram/Fluoxetine/Sertraline/Venlafaxine) + Aripiprazole</td>
</tr>
<tr>
<td>Fava,114 2005</td>
<td>SSRI + placebo</td>
<td>SSRI + Modafinil</td>
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<tr>
<td>Nemets,123 1999</td>
<td>SSRI + placebo (glucose)</td>
<td>SSRI + Inositol</td>
</tr>
<tr>
<td>Dunner,86 2007</td>
<td>Sertraline</td>
<td>Sertraline + Ziprasidone 60mg/d Sertraline + Ziprasidone 80mg/d</td>
</tr>
<tr>
<td>Appelberg,120 2001</td>
<td>SSRI + placebo</td>
<td>SSRI + Buspirone</td>
</tr>
<tr>
<td>Landén,97 1998 Landén,92 2005 Landén,130 1999</td>
<td>Citalopram or Paroxetine</td>
<td>Citalopram or Paroxetine + Buspirone</td>
</tr>
<tr>
<td>Rush,44 2006 Trivedi,113 2006 Thase,110 2007</td>
<td>Switching to new monotherapy (Sertraline/Venlafaxine/Buproprion/CBT)</td>
<td>Citalopram + Buspirone</td>
</tr>
<tr>
<td>Licht,119 2002</td>
<td>Sertraline Dose 1 + Placebo Sertraline Dose 2 + Placebo</td>
<td>Sertraline + Mianserin</td>
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<td>Ferreri,121 2001</td>
<td>Fluoxetine</td>
<td>Fluoxetine + Mianserin</td>
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<td>Baumann,124 1996</td>
<td>Citalopram + Placebo</td>
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<td>Bondolfi,112 2006</td>
<td>Paroxetine</td>
<td>Paroxetine + Lithium Switch to Venlafaxine</td>
</tr>
<tr>
<td>Fava,118 2002</td>
<td>Fluoxetine + Placebo</td>
<td>Fluoxetine + Lithium Fluoxetine + Desipramine</td>
</tr>
<tr>
<td>Fava,98 1994</td>
<td>Fluoxetine</td>
<td>Fluoxetine + Lithium Fluoxetine + Desipramine</td>
</tr>
<tr>
<td>Thase,88 2007</td>
<td>Fluoxetine Olanzapine</td>
<td>Fluoxetine + Olanzapine</td>
</tr>
<tr>
<td>Shelton,122 2001</td>
<td>Olanzapine + Placebo Fluoxetine + Placebo</td>
<td>Fluoxetine + Olanzapine</td>
</tr>
<tr>
<td>Keitner,95 2009</td>
<td>SSRI + Risperidone</td>
<td>SSRI + Risperidone</td>
</tr>
<tr>
<td>Mahmoud,108,2007</td>
<td>SSRI + Placebo</td>
<td>SSRI + Risperidone</td>
</tr>
<tr>
<td>Bauer134,188 2010</td>
<td>Any SSRI + Placebo</td>
<td>Any SSRI + Quetiapine XR 150 mg Any SSRI + Quetiapine XR 300 mg</td>
</tr>
<tr>
<td>Perry,93 2004</td>
<td>Fluoxetine/Setraline/Paroxetine + placebo (lactose powder)</td>
<td>Fluoxetine/Setraline/Paroxetine + Pindolol</td>
</tr>
<tr>
<td>Sokolski,186 2004</td>
<td>Paroxetine + Placebo</td>
<td>Paroxetine + Pindolol</td>
</tr>
</tbody>
</table>

**Buspirone**

**Mianserin**

**Lithium**

**Atypical Anti-psychotics**

**Pindolol**
Table 8. Monotherapy versus combined therapy studies showing the comparison and treatment interventions grouped by type of intervention (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiles, 94, 2008</td>
<td>Any SSRI</td>
<td>SSRI + CBT</td>
</tr>
<tr>
<td>Carta, 127, 2008</td>
<td>Any SSRI</td>
<td>SSRI + Exercise</td>
</tr>
<tr>
<td>Lynch, 128, 2007</td>
<td>Paroxetine/Sertraline/Fluoxetine</td>
<td>SSRI + DBT</td>
</tr>
<tr>
<td>Thase, 110, 2007</td>
<td>Switching to new monotherapy (Sertraline/</td>
<td>Citalopram + CBT</td>
</tr>
<tr>
<td></td>
<td>Venlaxfine/Buproprion/CBT)</td>
<td></td>
</tr>
<tr>
<td>Trivedi, 113, 2006</td>
<td>Increase Escitalopram dose + Education</td>
<td>Increase Escitalopram dose + Education + Interpersonal Therapy</td>
</tr>
<tr>
<td>Reynolds 133, 135, 137</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; SSRI = selective serotonin reuptake inhibitors
*Indicates that comparison arm is not the SSRI prior to the switch.

Outcomes
The majority of studies reported change scores as the primary outcome of choice. All but two studies used the MADRS, HAMD, BDI, or QID-SD-16 for at least one primary outcome; other outcomes used included the CGI, 92, 97, 114, 120, 130 and the WHOQOL Brief Psychiatric inventory. 127 Only three studies explicitly stated that remission was the primary outcome, defined as a MADRS total score of less than 10, 112 HAMD-17 score less than seven for 3 consecutive weeks, 133, 135, 137 or the QIDS-SR-16 score less than five. 44, 110, 113 All other studies either specified that the endpoint change score relative to baseline was the primary outcome, or did not report which measure was the primary one to evaluate efficacy.

Setting
The studies were conducted in Denmark and Iceland, 119 Switzerland, 112 France, 121 Italy, 82, 83, 127 Finland, 120 Norway and Sweden, 92, 97, 130 United Kingdom, 94 Israel, 89, 123 Canada, 86, 88, and United States. 44, 79, 80, 84, 86-88, 91, 93, 95, 96, 98, 101, 105, 108-110, 113, 114, 118, 122, 124, 126, 128, 131-135, 137 Three studies did not report the setting. 87, 88, 92, 97, 101, 130, 132 From the remaining 28, all studies included subjects from outpatient psychiatric, tertiary, or primary care settings with the exception of one study 124 that included patients with a minimum of 4 weeks inpatient hospitalization.

Risk of Bias Assessment
Figure 6 shows that method of randomization, compliance with treatment, and the role of the funder were at high risk of bias for over 75 percent of the 28 studies evaluating monotherapies versus combination therapies. Allocation concealment was not achieved by approximately 30 percent of studies. Overall, these studies would be categorized as having a moderate risk of bias.

Adherence with treatment was evaluated in only three studies 94, 112, 114 that reported some aspect of compliance with treatment; the remaining studies did not. A single study 120 from 28 employed a washout phase (2 weeks) prior to switching to the new treatment.
Table 9 shows the distribution of studies with respect to the source of funding. Eighteen studies were funded solely by industry and 10 solely by nonindustry sources. One study was funded by both, and five studies did not report the source of funding. As indicated in Figure 6, the role of the study sponsor was not clearly specified in approximately 75 percent of the 28 studies evaluated here.
Table 9. Sources of funding for studies evaluating monotherapies relative to combined therapies

<table>
<thead>
<tr>
<th>Funding Source</th>
<th>MONOTHERAPY*</th>
<th>COMBINED THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose or Duration Change</td>
<td>Switch to non-SSRI</td>
</tr>
<tr>
<td>Industry</td>
<td></td>
<td>Thase®88 Shelton®122 Licht®119 Ferreri®121 Bondolfi®112</td>
</tr>
<tr>
<td>Non-industry</td>
<td>Rush®44</td>
<td>Shapira®89 Fava®18 Trivedi®113 Fava®118 Baumann®124 Rush®44</td>
</tr>
<tr>
<td>Both</td>
<td></td>
<td>George®84</td>
</tr>
<tr>
<td>Not Reported</td>
<td></td>
<td>Seidman®191 Perry®93 Nemets®123 Sokolski®96 Altamura®82 Altamura®82 Altamura®82</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitors
*No studies reported: Switch to another SSRI, Switch to Augmenting Agent, or Switch to NonPharm.

Efficacy of Monotherapy Versus Combined Therapy

Outcomes of Response and Remission

Figures 7 to 10 and Table 10 detail the rates of response and remission reported within the studies in this grouping. The rates of response and remission for all studies cannot be directly compared across studies, as different primary outcomes were used and there is some variation in thresholds for these outcomes. Response was defined as 50 percent change from baseline in all but one study that used the HAMD, BDI, or the MADRS; one study using the HAMD defined response as a 30 percent change.98 Three studies92,97,114,120,130 using the CGI defined response as a change to “improved” or “very improved.” Three studies did not specify definitions for response or remission.89,123,127 Thresholds for remission for studies using the HAMD varied from seven to eight and for the MADRS less than 8 or 10. Only one study provided some data for partial responders (greater than 25 percent but less than 50 percent).88
Although the majority of studies that could be examined in this systematic review involved comparisons between monotherapy against combination therapy, the wide array of agents used in the combination treatments make identification of trends difficult.

In general, these studies involved one of two study designs. The most commonly employed design involved establishing a cohort of patients who had an inadequate response to an SSRI and then randomizing that group to either maintenance of the SSRI and placebo treatment or maintenance of the SSRI in combination with an active intervention. The “monotherapy” group therefore reflects patients who received ongoing treatment with an SSRI that had been deemed to be ineffective or inadequate at a specified point in treatment. Far fewer studies employed a design in which patients who had an inadequate response to an SSRI were then switched to another treatment and then compared against the combination of the original SSRI plus a new intervention. The STAR*D trial exemplified this latter type of design in which a portion of patients were switched to a new antidepressant treatment following an inadequate response to citalopram, while another portion remained on citalopram and had a second treatment added (buspirone, bupropion, or CBT).

In the STAR*D trial, the data did not confirm the noninferiority or superiority of either a switch to monotherapy or the addition of another treatment (Figure 8). Although not statistically significant, there appeared to be a slight, but consistent, favoring of the combination treatment approach. In another trial with a small number of participants, adding either citalopram or clomipramine to another SSRI resulted in greater rates of response compared to adding a placebo. The additional treatments were all provided by intravenous infusion over five days, however, and extrapolation of these results is problematic as oral preparations of the same compounds might not have resulted in a similar pattern of results.

The greatest number of studies in this comparison group involved the treatment strategies of adding an intervention or placebo to ongoing therapy with the SSRI to which patients had shown an inadequate response (Figures 7 and 10). Note that studies within these figures have been categorized by drug classes (SSRI, nonSSRI, augmenting agents, nonpharmacological). Additionally, we have grouped the studies using augmentation agents based on the number of trials per drug or drug class; interventions that had more than one study included lithium, buspirone, mianserin, atypical antipsychotics, and nonpharmacological therapies. Although there were two studies where pindolol was used as the augmenting agent, one did not provide response or remission rates for the monotherapy group.

For buspirone and the outcome of remission, we are limited to the different treatment arms of the STAR*D study (comparing sertraline relative to citalopram combined with buspirone), which showed a potentially small difference, but this was not for the outcome of response (see Figure 9). This may be an effect of the outcome used to define remission, as no advantage was seen for the QIDS-SR outcome. Studies evaluating the addition of mianserin show no relative advantage to the monotherapy comparator treatment for either the outcome of response or remission.

**Atypical Antipsychotics**

Overall, none of the augmenting agents showed any relative difference or advantage over the monotherapy comparator for the outcomes of benefit, with the exception of the atypical antipsychotics. Trials of fluoxetine in combination with olanzapine and risperidone in combination with SSRI treatment show some relative advantage over monotherapy in patients with MDD for both response and remission. Note that two studies provided subgroup data specific to the SSRI failed group. As such the studies were not randomized for this subgroup and
therefore balance between groups was not maintained. Two studies (five publications) indicated that patients on an SSRI combined with aripiprazole showed consistently greater MADRS total score relative to placebo (-8.6 versus -5.5 treatment difference -3.1, 95% CI: -4.5 to -1.7). Another two studies evaluated the use of quetiapine (at two different doses) as an augmenting agent and undertook a pooled analysis. This pooled analysis did not report response and remission rates but mean change scores for the SSRI subgroup (MADRS total scores at week 6 quetiapine XR 150 and 300mg/day, compared with placebo as adjunct to SSRIs [-14.8, -14.7 and -12.7, respectively; p<0.05, for each dose]).

Nonpharmacological Therapies

Evaluation of CBT as an add-on therapy showed no advantage when considering any monotherapy comparator; however, most of these data were derived from the STAR*D study. Similarly, a study in older adults showed no advantage of adding on interpersonal therapy to escitalopram.

Other Outcomes

Eight studies attempted to evaluate quality of life outcomes and some used more than one type of scale; all were selected as secondary outcome measures. Four studies used the Sheehan Disability Scale, four used the Endicott Enjoyment and Satisfaction Scale, and two also used some form of the SF36/SF12. The STAR*D also included a measure of work productivity. Note that four of these studies provided stratified findings for the SSRI failed subgroup; data for quality of life outcomes was not provided. All other studies showed no differences between groups for these outcomes.

Table 10. Summary of reported rates of response and remission for studies comparing monotherapy treatment to combined therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response* n (%)</th>
<th>p Value</th>
<th>Remission* n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adding SSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008</td>
<td>5 day</td>
<td>HAMD-21</td>
<td>18</td>
<td>SSRI + PBO (saline)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>SSRI + CIT 10mg in 250ml of saline</td>
<td>9 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adding Non-SSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008</td>
<td>5 day</td>
<td>HAMD-21</td>
<td>18</td>
<td>SSRI + PBO (saline)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>SSRI + CM 25mg in 250ml of saline (intravenous)</td>
<td>11 (61.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fava 2002</td>
<td>12</td>
<td>HAMD-17</td>
<td>33</td>
<td>FLX 40-60mg/d + PBO</td>
<td>14 (42.4)</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>FLX 20mg/d, DES 25-50mg/d</td>
<td>10 (29.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fava 1994</td>
<td>4</td>
<td>HAMD-17</td>
<td>15</td>
<td>FLX 40-60mg/d</td>
<td>8 (53)*</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>FLX 20mg + DES 25-50mg/d</td>
<td>3 (25)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Summary of reported rates of response and remission for studies comparing monotherapy treatment to combined therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response(^a) n (%)</th>
<th>p Value</th>
<th>Remission(^b) n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rush 2006(^44)</td>
<td>12</td>
<td>HAMD-17 QIDS-SR-16(^\ast)</td>
<td>238</td>
<td>SER 50-200mg/d</td>
<td>63 (26.7)(^*)</td>
<td>NR</td>
<td>42 (17.6)</td>
<td>63 (6.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>VEN 37.5-375mg/d</td>
<td>70 (28.2)(^*)</td>
<td></td>
<td>62 (24.8)</td>
<td>62 (24.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>239</td>
<td>BUP 150-400mg/d</td>
<td>62 (26.1)(^*)</td>
<td></td>
<td>51 (21.3)</td>
<td>61 (25.5)</td>
</tr>
<tr>
<td>Trivedi 2006(^113)</td>
<td>12</td>
<td>HAMD-17 QIDS-SR-16(^\ast)</td>
<td>279</td>
<td>CIT + BUP, 200-400mg/d</td>
<td>88 (31.8)(^*)</td>
<td></td>
<td>83 (29.7)</td>
<td>108 (38.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.93 0.16</td>
<td></td>
</tr>
<tr>
<td>Preskorn 2006(^80)</td>
<td>6</td>
<td>HAMD-NS</td>
<td>15</td>
<td>PAX 40mg + PBO</td>
<td>3 (20)</td>
<td>&lt;0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAX 40mg + CP-101,606 infusion/duration to 1.5 hours and the dose to 0.5mg/kg per hour</td>
<td>12 (80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>George 2008(^84)</td>
<td>8</td>
<td>HAMD-17</td>
<td>10</td>
<td>SSRI + PBO</td>
<td>1 (10)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>SSRI + ME, 5mg/d</td>
<td>5 (45.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adding Augmenting Agents**

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response(^a) n (%)</th>
<th>p Value</th>
<th>Remission(^b) n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson 2007(^87,101,132)</td>
<td>8</td>
<td>MPS</td>
<td>74</td>
<td>SER 100mg/d + PBO</td>
<td></td>
<td>28 (37.8)</td>
<td>0.865</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72</td>
<td>SER 100mg/d + AM 40mg/d</td>
<td></td>
<td>29 (40.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shapira 2006(^89)</td>
<td>4</td>
<td>HAMD-21</td>
<td>9</td>
<td>SSRI + PBO</td>
<td>7 (9)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>SSRI + PI</td>
<td>2 (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seidman 2005(^91)</td>
<td>6</td>
<td>HAMD-24</td>
<td>13</td>
<td>SSRI + PBO volume matched, (injection)</td>
<td>3 (23.1)</td>
<td>0.226</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13</td>
<td>SSRI + TE 200-600mg/d</td>
<td>7 (53.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berman 2007(^109)</td>
<td>8</td>
<td>MADRS</td>
<td>176</td>
<td>New SSRI + PBO</td>
<td>NR for SSRI subgroup</td>
<td></td>
<td>NR for SSRI subgroup</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>182</td>
<td>New SSRI + ARI, 5-15</td>
<td>NR for SSRI subgroup</td>
<td></td>
<td>NR for SSRI subgroup</td>
<td></td>
</tr>
<tr>
<td>Marcus 2008(^108,131)</td>
<td>8</td>
<td>MADRS</td>
<td>191</td>
<td>SSRI + PBO</td>
<td>NR for SSRI subgroup</td>
<td></td>
<td>NR for SSRI subgroup</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>190</td>
<td>SSRI + ARI 5-20mg/d (5-11mg ?)</td>
<td>NR for SSRI subgroup</td>
<td></td>
<td>NR for SSRI subgroup</td>
<td></td>
</tr>
<tr>
<td>Fava 2005(^114)</td>
<td>8</td>
<td>HAMD-17 CGI-I(^\ast)</td>
<td>153</td>
<td>SSRI + PBO</td>
<td>48 (32)(^*)</td>
<td>&gt;0.09</td>
<td>55 (36)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>158</td>
<td>SSRI + MOD 100-200</td>
<td>64 (41)(^*)</td>
<td></td>
<td>68 (44)</td>
<td></td>
</tr>
<tr>
<td>Nemets 1999(^123)</td>
<td>4</td>
<td>HAMD 24</td>
<td>18</td>
<td>SSRI original dose + PBO</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>IN 12gm/d, SSRI original dose;</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunner 2007(^86)</td>
<td>8</td>
<td>MADRS</td>
<td>20</td>
<td>SER 100-200mg/d</td>
<td>4 (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
<td>SER 100-200mg/d + ZI 40-80mg/d</td>
<td>6 (32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>SER 100-200mg/d + ZI 80-160mg/d</td>
<td>2 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Summary of reported rates of response and remission for studies comparing monotherapy treatment to combined therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response n (%)</th>
<th>p Value</th>
<th>Remission n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thase 2007</td>
<td>8</td>
<td>MADRS</td>
<td>203</td>
<td>FLX 50mg/d</td>
<td>34 (16.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>197</td>
<td>OLZ 6-18mg/d</td>
<td>29 (14.7)</td>
<td>0.012</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>198</td>
<td>OLZ 6-18mg/d + FLX50mg/d</td>
<td>54 (27.3)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shelton 2001</td>
<td>8</td>
<td>MADRS</td>
<td>8</td>
<td>FLX 20-60mg/d</td>
<td>1 (10)</td>
<td>0.006 vs. com</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>OLZ 5-20mg/d</td>
<td>0 (0)</td>
<td>0.003 vs. com</td>
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<td>10</td>
<td>OLZ 5-20mg/d, FLX 20-60mg/d</td>
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<tr>
<td>Mahmoud 2007</td>
<td>6</td>
<td>HAMD-17</td>
<td>74</td>
<td>SSRI + PBO</td>
<td>4 (5)</td>
<td></td>
<td>21 (25)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82</td>
<td>SSRI + RIS 0.25-1mg/d</td>
<td>4 (5)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Keitner 2009</td>
<td>4</td>
<td>MADRS</td>
<td>22</td>
<td>SSRI dose maintained + PBO</td>
<td>5 (22.7)</td>
<td>0.011</td>
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<td>47</td>
<td>RIS 0.5-3mg/d + antidepressant dose maintained</td>
<td>24 (51)</td>
<td></td>
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</tr>
<tr>
<td>Rush 2006</td>
<td>12</td>
<td>HAMD-17, QIDS-SR-16</td>
<td>238</td>
<td>SER 50-200mg/d</td>
<td>63 (26.7)</td>
<td>NR</td>
<td>42 (17.6)</td>
<td>63 (6.4)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>250</td>
<td>VEN 37.5-375mg/d</td>
<td>70 (28.2)</td>
<td>NR</td>
<td>62 (24.8)</td>
<td>62 (24.8)</td>
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<td>239</td>
<td>BUP 150-400mg/d</td>
<td>62 (26.1)</td>
<td>NR</td>
<td>51 (21.3)</td>
<td>61 (25.5)</td>
</tr>
<tr>
<td>Trivedi 2006</td>
<td>12</td>
<td>HAMD-17, QIDS-SR-16</td>
<td>286</td>
<td>CIT + BUS, 200-400mg/d</td>
<td>77 (27)</td>
<td>NR</td>
<td>86 (30.1)</td>
<td>94 (32.9)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>0.93 *</td>
<td></td>
<td>0.16 *</td>
<td></td>
</tr>
<tr>
<td>Appelberg 2001</td>
<td>6</td>
<td>MADRS</td>
<td>51</td>
<td>CIT 40mg/d/FLX 35.4mg/d + PBO</td>
<td>16 (31)</td>
<td>0.034</td>
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<tr>
<td>Landén 1996</td>
<td>4</td>
<td>CGI-S, CGI-I</td>
<td>60</td>
<td>CIT 46.1mg/d or PAX 39.8mg/d + PBO</td>
<td>28 (46.7)</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>57</td>
<td>CIT 46.1mg/d or PAX 39.8mg/d + BUS 49mg/d</td>
<td>29 (50.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fava 1994</td>
<td>4</td>
<td>HAMD-17</td>
<td>15</td>
<td>FLX 40-60mg/d</td>
<td>8 (53)</td>
<td>0.24</td>
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<tr>
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<td>14</td>
<td>FLX 20mg/d + LI 300-600mg/d</td>
<td>4 (29)</td>
<td></td>
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<tr>
<td>Fava 2002</td>
<td>12</td>
<td>HAMD-17</td>
<td>33</td>
<td>FLX 40-60mg/d + PBO</td>
<td>14 (42.4)</td>
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<td></td>
<td></td>
<td>34</td>
<td>FLX 20mg/d, LI 300-600mg/d</td>
<td>8 (23.5)</td>
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<tr>
<td>Baumann 1996</td>
<td>4</td>
<td>HAMD-21</td>
<td>14</td>
<td>CIT 40-60mg/d</td>
<td>2 (14)</td>
<td>0.05</td>
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<td></td>
<td>10</td>
<td>CIT 40-60mg/d, LI 800mg/d;</td>
<td>6 (60)</td>
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<tr>
<td>Bondolfi 2006</td>
<td>4</td>
<td>MADRS</td>
<td>19</td>
<td>PAX 40mg/d</td>
<td>2 (10.5)</td>
<td>NR</td>
<td>3 (15.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>VEN 150mg/d</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<td></td>
<td></td>
<td></td>
<td>13</td>
<td>PAX 30mg/d + LI</td>
<td>1 (7.8)</td>
<td></td>
<td>0 (0)</td>
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</tr>
</tbody>
</table>

* p-values are for comparisons with placebo or other treatments.
Table 10. Summary of reported rates of response and remission for studies comparing monotherapy treatment to combined therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response a n (%)</th>
<th>p Value</th>
<th>Remission b n (%)</th>
<th>p Value</th>
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<tbody>
<tr>
<td><strong>Adding Pindolol</strong></td>
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<td></td>
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<tr>
<td>Perry 200493</td>
<td>6</td>
<td>HAMD</td>
<td>17</td>
<td>SSRI + PBO FLX 20-60mg, PARO20-40mg, SER 50mg</td>
<td>6 (35.2)</td>
<td>1</td>
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<td></td>
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<td></td>
<td></td>
<td>SSRI + PI Total = only SSRI doses given, PI dose not reported; Group 1 = FLX 20-60mg, PAX 20mg, SER 150-200mg</td>
<td>5 (23.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sokolski 200496</td>
<td>4</td>
<td>HAMD</td>
<td>5</td>
<td>PAX 40mg/d + PBO</td>
<td>NR</td>
<td>0.001</td>
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<td></td>
<td>PAX 40mg/d + PI 7.5mg/d</td>
<td>3 (75)</td>
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<td><strong>Adding MIN</strong></td>
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<tr>
<td>Licht 2002119</td>
<td>6</td>
<td>HAMD-NS</td>
<td>99</td>
<td>SER 100mg/d + PBO</td>
<td>69 (70)</td>
<td>0.64</td>
<td>37 (38)</td>
<td>0.38</td>
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<td>SER 200mg/d + PBO</td>
<td>54 (64)</td>
<td>0.03</td>
<td>28 (29)</td>
<td>0.19</td>
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<tr>
<td>Ferreri 2001121</td>
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<td>HAMD 17</td>
<td>38</td>
<td>FLX 20mg/d</td>
<td>14 (37)</td>
<td>0.1</td>
<td>14 (36)</td>
<td>0.06</td>
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<td></td>
<td>MIN 60mg/d</td>
<td>16 (48.5)</td>
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<td>6 (18)</td>
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<td></td>
<td>FLX 20mg/d + MIN 60-60mg/d</td>
<td>20 (62.5)</td>
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<td>14 (44)</td>
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<tr>
<td><strong>Adding Non-Pharmacological</strong></td>
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<tr>
<td>Carta 2006127</td>
<td>32</td>
<td>WHOQOL-Bref</td>
<td>10</td>
<td>SSRI</td>
<td>NR</td>
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<td>NR</td>
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<td></td>
<td></td>
<td>SSRI + Exercise</td>
<td>NR</td>
<td></td>
<td>NR</td>
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<tr>
<td>Lynch 2007128</td>
<td>54</td>
<td>HAMD-NS</td>
<td>12</td>
<td>SSRI</td>
<td>6 (50)</td>
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<td>SSRI + DBT</td>
<td>12 (60)</td>
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<tr>
<td>Wiles 200854</td>
<td>16</td>
<td>BDI</td>
<td>9</td>
<td>SSRI</td>
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<td></td>
<td>SSRI + CBT</td>
<td>8 (56)</td>
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<tr>
<td>Reynolds 2010137</td>
<td>10</td>
<td>SCID/DSM-IV</td>
<td>60</td>
<td>SSRI + IPT</td>
<td>49 (62)</td>
<td>0.20</td>
<td>35 (58)</td>
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<td></td>
<td>SSRI</td>
<td>49(77)</td>
<td></td>
<td>29(45)</td>
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</table>
Table 10. Summary of reported rates of response and remission for studies comparing monotherapy treatment to combined therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response a n (%)</th>
<th>p Value</th>
<th>Remission b n (%)</th>
<th>p Value</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Rush 2006&lt;sup&gt;a&lt;/sup&gt;</th>
<th>12</th>
<th>HAMD-17, QIDS-SR-16&lt;sup&gt;b&lt;/sup&gt;</th>
<th>238</th>
<th>SER 50-200mg/d</th>
<th>63 (26.7)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>NR</th>
<th>42 (17.6) 63 (6.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>VEN 37.5-375mg/d</td>
<td>70 (28.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>62 (24.8) 62 (24.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>239</td>
<td>BUP 150-400mg/d</td>
<td>62 (26.1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>51 (21.3) 61 (25.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36</td>
<td>Medications Monotherapy</td>
<td>8 (22.2)</td>
<td></td>
<td>9 (25) 11 (30.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>86</td>
<td>CBT</td>
<td>23 (26.7)</td>
<td></td>
<td>24 (27.9) 24 (27.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65</td>
<td>CIT + CBT</td>
<td>23 (35.4)</td>
<td></td>
<td>15 (23) 20 (20.7)</td>
</tr>
</tbody>
</table>

AM = atomoxetine; ARI = aripiprazole; BDI = Beck Depression Inventory; BUP = bupropion; BUS = buspirone; CBT = cognitive behavioral therapy; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity scale; CIT = citalopram; CM = clomipramine; DES = desipramine; DLX = duloxetine; FLX = fluoxetine; HAMD = Hamilton Depression Rating Scale; HAMD-NS = Hamilton Depression Rating Scale not specified; LI = lithium; MADRS = Montgomery-Åsberg Depression Rating Scale; ME = mecamyline hydrochloride; MIN = mianserin; MOD = modafinil; MPS = Maier Philipp core mood severity subscale; NR = not reported; NS = not significant; NT = not tested; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PI = pindolol; PLZ = phenelzine; QIDS-SR16 = Quick Inventory of Depressive Symptoms Self Report (16) RIS = risperidone; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; TCP = tranylcypromine; TE = testosterone; VEN = venlafaxine; VEN-ER = venlafaxine extended release; WHOQOL-Bref = World Health Organization Quality of Life 26 item scale; ZI = ziprasidone

<sup>a</sup>Response was defined as 50 percent change relative to baseline unless noted within the table.

<sup>b</sup>Remission was defined as the standard threshold value for the particular outcome.

<sup>c</sup>The QIDS-SR reported outcomes.
Figure 7. Forest plot showing monotherapy versus combined therapy for the outcome of response for augmenting agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>No. of events</th>
<th>Combined Therapy</th>
<th>Monotherapy</th>
</tr>
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<td><strong>Mixed Agents</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Preskorn 2008* (PAX + PBO vs. PAX + CP, H)</td>
<td>4.00 (1.41, 11.35)</td>
<td>12/15</td>
<td>3/15</td>
<td></td>
</tr>
<tr>
<td>George 2008* (SSRI + PBO vs. SSRI + ME, H-17)</td>
<td>4.55 (1.63, 12.56)</td>
<td>5/11</td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td>Shapira 2008* (SSRI + PBO vs. SSRI + PHN, H-21)</td>
<td>0.23 (0.06, 0.86)</td>
<td>2/11</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Fava 2003** (SSRI + PBO vs. SSRI + MOD, CG)</td>
<td>1.20 (0.96, 1.69)</td>
<td>64/106</td>
<td>48/153</td>
<td></td>
</tr>
<tr>
<td>Dunnar 2007** (SEER vs. SER + CP, M)</td>
<td>1.43 (1.07, 1.93)</td>
<td>4/21</td>
<td>4/20</td>
<td></td>
</tr>
<tr>
<td>Dunnar 2007** (SER vs. SER + CP, M)</td>
<td>0.53 (0.11, 2.55)</td>
<td>2/19</td>
<td>4/20</td>
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</tr>
<tr>
<td><strong>Adding Atypical Antipsychotics</strong></td>
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<tr>
<td>Thase 2007** (OLZ + FLX, M)</td>
<td>1.37 (1.04, 1.97)</td>
<td>80/198</td>
<td>60/235</td>
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</tr>
<tr>
<td>George 2008* (SSRI + PBO vs. SSRI + ME, H-17)</td>
<td>1.56 (1.17, 2.06)</td>
<td>80/199</td>
<td>55/187</td>
<td></td>
</tr>
<tr>
<td>Shapira 2006** (SSRI + PBO vs. SSRI + PHN, H-21)</td>
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<td>2/11</td>
<td>7/9</td>
<td></td>
</tr>
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<td>Fava 2005** (SSRI + PBO vs. SSRI + MOD, CG)</td>
<td>1.29 (0.96, 1.74)</td>
<td>64/106</td>
<td>48/153</td>
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<td>4/21</td>
<td>4/20</td>
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<tr>
<td>Dunnar 2007** (SER vs. SER + CP, M)</td>
<td>0.53 (0.11, 2.55)</td>
<td>2/19</td>
<td>4/20</td>
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<tr>
<td><strong>Adding Buspirone</strong></td>
<td></td>
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<tr>
<td>Thase 2007** (FLX + PLX + OLZ, M)</td>
<td>1.70 (1.30, 2.21)</td>
<td>57/171</td>
<td>60/171</td>
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<td>George 2008* (SSRI + PBO vs. SSRI + ME, H-17)</td>
<td>1.56 (1.17, 2.06)</td>
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<td>48/153</td>
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<td>Dunnar 2007** (SEER vs. SER + CP, M)</td>
<td>1.43 (1.07, 1.93)</td>
<td>4/21</td>
<td>4/20</td>
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<tr>
<td>Dunnar 2007** (SER vs. SER + CP, M)</td>
<td>0.53 (0.11, 2.55)</td>
<td>2/19</td>
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<td><strong>Adding Lithium</strong></td>
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<tr>
<td>Thase 2004** (FLX + PLX + OLZ, M)</td>
<td>0.54 (0.21, 1.39)</td>
<td>4/14</td>
<td>8/15</td>
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<td>George 2008* (SSRI + PBO vs. SSRI + ME, H-17)</td>
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<td>2/19</td>
<td>4/20</td>
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<tr>
<td><strong>Adding Pindolol</strong></td>
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</tr>
<tr>
<td>Perry 2004** (PAX + PBO vs. PAX + LI, H-17)</td>
<td>0.67 (0.25, 1.83)</td>
<td>5/21</td>
<td>6/17</td>
<td></td>
</tr>
<tr>
<td><strong>Adding Mianserin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Licht 2002** (SER + PBO vs. SER + MIN, H-NS)</td>
<td>0.97 (0.80, 1.17)</td>
<td>69/95</td>
<td>69/95</td>
<td></td>
</tr>
<tr>
<td>Licht 2002** (SER + PBO vs. SER + MIN, H-NS)</td>
<td>1.22 (1.08, 1.36)</td>
<td>54/98</td>
<td>54/98</td>
<td></td>
</tr>
<tr>
<td>Ferreri 2001** (PAX + PBO vs. PAX + MIN, H-17)</td>
<td>1.70 (1.03, 2.76)</td>
<td>20/32</td>
<td>14/36</td>
<td></td>
</tr>
<tr>
<td>Bondolfi 2006** (VEN vs. PAX + LI, H-17)</td>
<td>0.41 (0.03, 10.32)</td>
<td>0/9</td>
<td>1/13</td>
<td></td>
</tr>
</tbody>
</table>

BUP = bupropion; BUS = buspirone; CG = Clinical Global Impressions-Improvement (CGI-I) Scale; CIT = citalopram; CP = CP 101,106 (NMDA receptor antagonist); FLX = fluoxetine; H = Hamilton Depression Rating Scale; H-17 = Hamilton Depression Rating Scale – 17 item; H-21 = Hamilton Depression Rating Scale – 21 item; H = Hamilton Depression Rating Scale; LI = lithium; M = Montgomery-Asberg Depression Rating Scale (MADRS); ME = mecamylamine hydrochloride; MIN = mianserin; MOD = modafinil; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PHN = phenytoin; PI = pindolol; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); RIS = risperidone; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; VEN = venlafaxine; Z80 = ziprasidone 80mg; Z160 = ziprasidone 160mg

*Represent STAR*D studies.
Figure 8. Forest plot of monotherapy versus combined therapies for the outcome of response for all interventions but augmenting agents

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Events, Combined Therapy</th>
<th>Events, Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding Non-Pharmacological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiles 2008 (SSRI vs. SSRI + CBT, B)</td>
<td>15.00 (0.97, 231.84)</td>
<td>7/10</td>
<td>0/10</td>
</tr>
<tr>
<td>Reynolds 2010 (SSRI + IPT, DSM-IV)</td>
<td>1.07 (0.89, 1.28)</td>
<td>49/60</td>
<td>49/64</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (SER vs. CIT + CBT, Q-16)</td>
<td>1.34 (0.90, 1.98)</td>
<td>23/65</td>
<td>63/238</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (VEN vs. CIT + CBT, Q-16)</td>
<td>1.26 (0.86, 1.86)</td>
<td>23/65</td>
<td>70/250</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (BUP vs. CIT + CBT, Q-16)</td>
<td>1.36 (0.92, 2.02)</td>
<td>23/65</td>
<td>62/239</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (CBT vs. CIT + CBT, Q-16)</td>
<td>1.59 (0.80, 3.19)</td>
<td>23/65</td>
<td>8/36</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (Med vs. CIT + CBT, Q-16)</td>
<td>1.32 (0.82, 2.14)</td>
<td>23/65</td>
<td>23/86</td>
</tr>
<tr>
<td>Adding SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008 (SSRI + PBO vs. SSRI + CIT, H-21)</td>
<td>19.00 (1.19, 303.76)</td>
<td>9/18</td>
<td>0/18</td>
</tr>
<tr>
<td>Adding Non SSRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008 (SSRI + PBO vs. SSRI + CM, H-21)</td>
<td>23.00 (1.46, 363.07)</td>
<td>11/18</td>
<td>0/18</td>
</tr>
<tr>
<td>Fava 2002 (FLX + PBO vs. FLX + DES, H-17)</td>
<td>0.69 (0.36, 1.33)</td>
<td>10/34</td>
<td>14/33</td>
</tr>
<tr>
<td>Fava 1994 (FLX vs. FLX + DES, H-17)</td>
<td>0.47 (0.16, 1.39)</td>
<td>3/12</td>
<td>8/15</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (SER vs. CIT + BUP, Q-16)</td>
<td>1.19 (0.91, 1.57)</td>
<td>88/279</td>
<td>63/238</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (VEN vs. CIT + CBT, Q-16)</td>
<td>1.13 (0.87, 1.47)</td>
<td>88/279</td>
<td>70/250</td>
</tr>
<tr>
<td><em>Rush 2006</em>/†Trivedi 2006* (BUP vs. CIT + CBT, Q-16)</td>
<td>1.22 (0.92, 1.60)</td>
<td>88/279</td>
<td>62/239</td>
</tr>
</tbody>
</table>

Abbreviations: B = Beck Depression Inventory; BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; CM = clomipramine; DES = desipramine; DSM-IV = the Diagnostic and Statistical Manual of Mental Disorders – 4th edition; FLX = fluoxetine; H-17 = Hamilton Depression Rating Scale – 17 item; H-21 = Hamilton Depression Rating Scale – 21 item; IPT = interpersonal therapy; Med = medication; PBO = placebo; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; SSRI = selective serotonin reuptake inhibitors; VEN = venlafaxine

*Represent STAR*D studies.
Figure 9. Forest plot of monotherapy versus combined therapy for augmenting agents for the outcome of remission

Study | Risk ratio (95% CI) | No. of events | Favors Monotherapy | Favors Combined Therapy
--- | --- | --- | --- | ---
Mixed Agents
Michelson 2007 | 1.06 (0.71, 1.60) | 29/72 | 28/74 | 0.016292
Fava 2005 | 1.20 (0.91, 1.58) | 68/158 | 55/153

Adding Atypical Antipsychotics
Thase 2007 | 1.63 (1.11, 2.39) | 54/198 | 34/203 | 61.3791
Thase 2007 | 1.85 (1.23, 2.78) | 54/198 | 29/197
Mahmoud 2007 | 4.74 (1.70, 13.17) | 21/82 | 4/74
Keitner 2009 | 2.25 (0.99, 5.10) | 24/47 | 5/22

Adding Buspirone
*Rush 2006 | 1.70 (1.23, 2.36) | 86/286 | 42/238
*Rush 2006 | 1.21 (0.92, 1.60) | 86/286 | 62/250
*Rush 2006 | 1.41 (1.04, 1.90) | 86/286 | 51/239
*Rush 2006 | 1.24 (0.95, 1.62) | 94/286 | 63/238
*Rush 2006 | 1.33 (1.01, 1.74) | 94/286 | 62/250
*Rush 2006 | 1.29 (0.98, 1.69) | 94/286 | 61/239

Adding Lithium
Bondolfi 2006 | 0.29 (0.02, 5.01) | 0/9 | 3/19
Bondolfi 2006 | (Excluded) | 0/9 | 0/13

Adding Mianserin
Licht 2002 | 1.17 (0.84, 1.65) | 43/98 | 37/99
Licht 2002 | 1.54 (1.05, 2.26) | 43/98 | 28/98

Abbreviations: AM = atomoxetine; BUP = bupropion; BUS = buspirone; CIT = citalopram; FLX = fluoxetine; H-17 = Hamilton Depression Rating Scale – 17 item; H = Hamilton Depression Rating Scale; LI = lithium; M = Montgomery-Asberg Depression Rating Scale (MADRS); MIN = mianserin; MOD = modafinil; MPS = Maier Philipp core mood severity subscale; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); RIS = risperidone; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; VEN = venlafaxine

*Represent STAR*D studies.
Figure 10. Forest plots for monotherapy versus combined therapies for all non-augmenting interventions for the outcome of remission

Monotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Events, Combined Therapy</th>
<th>Events, Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch 2007* (SSRI vs. SSRI + DBT, H)</td>
<td>1.20 (0.61, 2.34)</td>
<td>12/20</td>
<td>6/12</td>
</tr>
<tr>
<td>Reynolds 2010* (SSRI + IPT, DSM-IV)</td>
<td>1.19 (0.84, 1.69)</td>
<td>35/65</td>
<td>29/64</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (SER vs. CIT + CBT, H-17)</td>
<td>1.31 (0.78, 2.20)</td>
<td>15/65</td>
<td>42/238</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (VEN vs. CIT + CBT, H-17)</td>
<td>0.93 (0.57, 1.52)</td>
<td>15/65</td>
<td>62/250</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (BUP vs. CIT + CBT, H-17)</td>
<td>1.08 (0.65, 1.79)</td>
<td>15/65</td>
<td>51/239</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (CBT vs. CIT + CBT, H-17)</td>
<td>0.92 (0.45, 1.89)</td>
<td>15/65</td>
<td>9/36</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (MME vs. CIT + CBT, H-17)</td>
<td>0.83 (0.47, 1.45)</td>
<td>15/65</td>
<td>24/86</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (SER vs. CIT + CBT, Q-16)</td>
<td>1.16 (0.76, 1.77)</td>
<td>20/65</td>
<td>63/238</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (VEN vs. CIT + CBT, Q-16)</td>
<td>1.24 (0.81, 1.90)</td>
<td>20/65</td>
<td>62/250</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (BUP vs. CIT + CBT, Q-16)</td>
<td>1.21 (0.79, 1.84)</td>
<td>20/65</td>
<td>61/239</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (CBT vs. CIT + CBT, Q-16)</td>
<td>1.01 (0.55, 1.86)</td>
<td>20/65</td>
<td>11/36</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (MME vs. CIT + CBT, Q-16)</td>
<td>1.10 (0.67, 1.81)</td>
<td>20/65</td>
<td>24/86</td>
</tr>
</tbody>
</table>

Adding Non SSRI Antidepressants

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>Events, Combined Therapy</th>
<th>Events, Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (SER vs. CIT + BUP, H-17)</td>
<td>1.69 (1.21, 2.34)</td>
<td>83/279</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (VEN vs. CIT + BUP, H-17)</td>
<td>1.20 (0.91, 1.59)</td>
<td>83/279</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (BUP vs. CIT + BUP, H-17)</td>
<td>1.39 (1.03, 1.89)</td>
<td>83/279</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (SER vs. CIT + BUP, Q-16)</td>
<td>1.46 (1.13, 1.89)</td>
<td>108/279</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (VEN vs. CIT + BUP, Q-16)</td>
<td>1.56 (1.20, 2.03)</td>
<td>108/279</td>
</tr>
<tr>
<td><em>Rush 2006</em>*/Trivedi 2006** (BUP vs. CIT + BUP, Q-16)</td>
<td>1.52 (1.17, 1.97)</td>
<td>108/279</td>
</tr>
</tbody>
</table>

BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; DBT = dialectical behavior therapy; DSM-IV = the Diagnostic and Statistical Manual of Mental Disorders – 4th edition; H-17 = Hamilton Depression Rating Scale – 17 item; H = Hamilton Depression Rating Scale; IPT = interpersonal therapy; Med = medication; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; SSRI = selective serotonin reuptake inhibitors; VEN = venlafaxine

*Represent STAR*D studies.
Combined Therapy Versus Combined Therapy Interventions

There were six studies\(^86,98,110,113,118,125,125\) with treatment arms that compared combination therapies with each other. All studies were RCTs with the exception of one study which did not randomize subjects, and the STAR*D study.\(^44,113\) The STAR*D cohort\(^110,113\) for level 2 subjects evaluated three combined therapy interventions and only these arms (citalopram plus CBT with two combined drug therapy interventions) are compared in this section. Two studies\(^86,125\) compared different doses of the same combination drug therapies.

In total there were 832 participants in the treatment arms evaluating combined interventions and the sample sizes varied from 11\(^125\) to 650 participants.\(^110,113\) The sample sizes per treatment arm varied from 5 subjects\(^125\) to 286 subjects.\(^113\) One study\(^44,110\) exceeded a total sample size of 101 and two studies\(^98,125\) had less than 30 subjects.

Overview of Study PICOT Characteristics

Population

The proportion of women in the sample varied from 47 percent,\(^86,118\) between 50 and 62 percent,\(^98,115,125\) and greater than 70 percent.\(^82,83\) Racial composition was not reported in four studies;\(^82,83,98,118,125\) two studies reporting ethnicity had approximately 78 percent\(^110,113\) and over 90 percent\(^86\) of the participants of the white race. Mean age of study subjects varied from 40 to 44 years in four studies,\(^86,98,110,113,118\) and ages ranged from 37 to 59 years,\(^125\) and 51 to 58 years\(^82,83\) in the remaining studies.

Inadequate Response

Table 11 shows the manner in which failure to respond to an SSRI had been established. Three studies\(^82,83,98,125\) determined failure retrospectively, and study subjects were currently on the same SSRI prior to the switch to the new intervention. In the three studies that determined inadequate response prospectively, fluoxetine,\(^118\) citalopram,\(^110,113\) and sertraline\(^86\) were the SSRIs for which failure was established. No study evaluated subjects specifically for prospective failed response to escitalopram, paroxetine, or fluvoxamine alone.

Table 11. Method of establishing failure to SSRI in studies comparing combination therapies to other combination therapies

<table>
<thead>
<tr>
<th>Determining Inadequate Response</th>
<th>Add Augmentor</th>
<th>Add Other SSRI</th>
<th>Add non-SSRI AD</th>
<th>Add Nonpharm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Trivedi(^113)*</td>
<td>Trivedi(^113)*</td>
<td>Thase(^110)*</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Fava(^118)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Dunner(^98)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SSRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Retrospective</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently on an SSRI or other AD</td>
<td>Fava(^98)</td>
<td>Altamura(^82,83)</td>
<td>Altamura(^98)</td>
<td></td>
</tr>
</tbody>
</table>

AD = antidepressant; SSRI = selective serotonin reuptake inhibitors

\*STAR*D study.
Mental Health History

Table 12 shows that five studies used the HAMD 17 or 21 item instruments to evaluate baseline severity; one study did not report baseline scores.

It is notable that several studies included patients of mild to moderate severity based on the HAMD criteria, while others included patients with marked depression. The number of previous depressive episodes were reported as a median of seven to eight (range 12 to 15) in the STAR*D cohort and not reported in five studies.

Table 12. Distribution of baseline scores for primary outcomes as a proxy for severity of MDD

<table>
<thead>
<tr>
<th>Disease-Specific Scale</th>
<th>Baseline Score 10 - 14</th>
<th>Baseline Score 15 - 19</th>
<th>Baseline Score 20 - 25</th>
<th>Baseline Score 26 - 30</th>
<th>Baseline Score &gt;31</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD-NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD-31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD-24</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAMD-21</td>
<td></td>
<td></td>
<td>Altamura\textsuperscript{82}</td>
<td>Altamura\textsuperscript{83}</td>
<td></td>
</tr>
<tr>
<td>HAMD-17</td>
<td>Trivedi\textsuperscript{113}</td>
<td>Rush\textsuperscript{44}</td>
<td>Thase\textsuperscript{110}</td>
<td>Fava\textsuperscript{98}</td>
<td>Fava\textsuperscript{118}</td>
</tr>
<tr>
<td>QIDS-SR16</td>
<td>Trivedi\textsuperscript{113}</td>
<td>Rush\textsuperscript{44}</td>
<td>Thase\textsuperscript{110}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BDI = Beck Depression Inventory; HAMD = Hamilton Depression Rating Scale; HAMD-NS = Hamilton Depression Rating Scale not specified; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS-SR16 = Quick Inventory of Depressive Symptoms Self Report (16).

Note that one study did not provide baseline scores and some studies provided scores for more than one instrument. No study in this grouping reported baseline use of CAM at baseline or endpoint.

Intervention

All but one study employed an RCT design and the STAR*D is considered a CCT. The STAR*D cohort for level 2 subjects, evaluated three combined therapy interventions and only these arms are compared in this section. Two studies compared two doses of the same combination therapy. Table 13 shows the duration of the study intervention. Two studies evaluated combined therapy for approximately one week, and the remaining studies varied treatment length from 4 to 12 weeks.
Table 13. Details of the length of the run-in and treatment phases for all studies

<table>
<thead>
<tr>
<th>Length of Treatment</th>
<th>2/3 Weeks</th>
<th>4/5 Weeks</th>
<th>6 Weeks</th>
<th>8 Weeks</th>
<th>&gt;8 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective Failure Run-In Phase</td>
<td></td>
<td></td>
<td>Dunner\textsuperscript{86}</td>
<td>Fava\textsuperscript{118}</td>
<td>Trivedi\textsuperscript{113} Rush\textsuperscript{44} Thase\textsuperscript{110}</td>
</tr>
<tr>
<td>Prospective Failure Treatment Phase</td>
<td></td>
<td>Fava\textsuperscript{118}</td>
<td>Dunner\textsuperscript{86}</td>
<td></td>
<td>Trivedi\textsuperscript{113} Rush\textsuperscript{44} Thase\textsuperscript{110}</td>
</tr>
<tr>
<td>Retrospective Failure Studies</td>
<td>Dinan\textsuperscript{82}# Altamura\textsuperscript{82,83}#</td>
<td></td>
<td>Fava\textsuperscript{98}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{#}Indicates treatment was for one week.
\textsuperscript{##}Indicates treatment was for 5 days.

Table 14 shows the types of combination therapies evaluated in these six studies. Two studies included an arm evaluating the nonSSRI desipramine,\textsuperscript{98,118} and one each evaluating clomipramine\textsuperscript{82,83} and bupropion.\textsuperscript{113} The augmenting agents used in these studies included buspirone, lithium, and ziprasidone. Two studies\textsuperscript{86,125} compared different doses of the same combination studies involving sertraline with either lithium and ziprasidone. The doses for both lithium (400-800mg) and ziprasidone (60 mg and 80 mg) are in the low to moderate range. It is unlikely that lithium at 400mg/d would result in therapeutic blood levels, but low doses of lithium have been commonly employed in augmentation trials. The STAR*D cohort compared two drug combination therapies with citalopram or CBT.\textsuperscript{110,113}

Table 14. Combined therapy versus combined therapy studies showing the comparison and treatment interventions grouped by type of intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Combined Therapy 1</th>
<th>Combined Therapy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altamura 2008\textsuperscript{82}</td>
<td>SSRI + Citalopram (intravenous)</td>
<td>SSRI + Clomipramine (intravenous)</td>
</tr>
<tr>
<td>Altamura 2008\textsuperscript{83}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rush 2006\textsuperscript{44}</td>
<td>Citalopram + Buproprion</td>
<td>Citalopram + Buspirone</td>
</tr>
<tr>
<td>Trivedi 2006\textsuperscript{113}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase 2007\textsuperscript{110}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Add Augmenting Agent

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinan 1993\textsuperscript{125}</td>
<td>Sertraline + Lithium 400mg</td>
</tr>
<tr>
<td>Dunner 2007\textsuperscript{86}</td>
<td>Sertraline + Ziprasidone 60mg/d</td>
</tr>
<tr>
<td>Fava 2002\textsuperscript{118}</td>
<td>Fluoxetine + Desipramine</td>
</tr>
<tr>
<td>Fava 1994\textsuperscript{98}</td>
<td>Fluoxetine + Lithium</td>
</tr>
</tbody>
</table>

Adding Nonpharmacological Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thase 2007\textsuperscript{110}</td>
<td>Citalopram + Buspirone</td>
</tr>
<tr>
<td>Rush 2006\textsuperscript{44}</td>
<td>Citalopram + CBT</td>
</tr>
<tr>
<td>Trivedi 2006\textsuperscript{113}</td>
<td>Citalopram + CBT</td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors

**Outcome**

A single study\textsuperscript{110,113} specified that remission was the primary outcome. All other studies indicated that the change or endpoint score was the primary outcome.
Setting
The six studies were conducted in the United Kingdom, Italy, Canada, and the United States (four studies). All studies included subjects in outpatient psychiatric or outpatient primary care.

Risk of Bias
Figure 11 shows that studies evaluating combined therapies were at high risk of bias for randomization, reporting compliance, and balancing prognostic indicators. The role of the funder was clarified in all studies and funding for the studies came from nonindustry sources in three studies, industry in one study, and two did not report the source. Overall these studies would be categorized as having a moderate level of risk of bias. None of the studies employed a washout phase or monitored compliance of subjects.

Figure 11. Percent of studies achieving risk of bias using the risk of bias tool criteria for studies evaluating combined therapies relative to combined therapies

Efficacy of Combined Therapy Versus Combined Therapy

Response and Remission
Table 15 and Figures 12 and 13 report the rates of response and remission for studies evaluating combined treatments relative to other combined treatments. Figure 12 illustrates that when the combination of citalopram plus buspirone was compared against the combination of citalopram and CBT, there was a nonsignificant pattern favoring the combination of medications in the STAR*D trial. There appeared to be no differences between combinations of therapies in
this large trial. When considering speed of response, there was a significant difference of 15 days for the group with CBT augmentation and only for the outcome of remission (p = 0.022).

**Other Outcomes**

The STAR*D study was the single trial to include quality of life measures and showed no significant differences between groups.
Table 15. Summary of reported rates of response and remission for studies evaluating combined therapy to other combined therapy treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Wks)</th>
<th>Rating Scale</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Response% n (%)</th>
<th>p Value</th>
<th>Remission% n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adding Non-SSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008*82,83</td>
<td>5 days</td>
<td>HAMD-21</td>
<td>18</td>
<td>SSRI+CIT 10mg in 250ml of saline</td>
<td>9 (50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18</td>
<td>SSRI+ CM 25mg in 250ml of saline (intravenous)</td>
<td>11 (61.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivedi 2006113</td>
<td>12</td>
<td>HAMD-17 QIDS-SR-16*</td>
<td>28</td>
<td>CIT +BUS 15-60mg/d</td>
<td>77*</td>
<td>86 (30.1)</td>
<td>94 (32.9)*</td>
<td>0.93 0.16*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>CIT +BUP, 200-400mg/d</td>
<td>62 (22.2)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Augmenting Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinan 1993125</td>
<td>1</td>
<td>HAMD-NS</td>
<td>6</td>
<td>SER 100-200mg/d + LI 400mg/d</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>SER 100-200mg/d + LI 800mg/d</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunner 200786</td>
<td>8</td>
<td>MADRS</td>
<td>21</td>
<td>SER 100-200 mg/d + ZI 40-80mg/d</td>
<td>6 (32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>SER 100-200 mg/d + ZI 80-160mg/d</td>
<td>2 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fava 2002118</td>
<td>12</td>
<td>HAMD-17</td>
<td>34</td>
<td>FLX 40-60mg/d + placebo DES</td>
<td>10 (29.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>FLX 20mg/d, LI 300-600mg/d</td>
<td>8 (23.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fava 199488</td>
<td>4</td>
<td>HAMD-17</td>
<td>12</td>
<td>FLX 20mg + DES 25-50mg/d</td>
<td>3 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>FLX 20mg/d + LI 300-600mg/d</td>
<td>4 (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adding Nonpharmacological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trivedi 2006113 Thase 2007110</td>
<td>12</td>
<td>HAMD-17 QIDS-SR-16*</td>
<td>28</td>
<td>CIT + BUS 15-60mg/d</td>
<td>77 (27)*</td>
<td>83 (29.7)</td>
<td>94 (32.8)*</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23</td>
<td>CIT + BUP, 200-400mg/d</td>
<td>62 (26.1)*</td>
<td>94 (39.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase 2007110</td>
<td>12</td>
<td>HAMD-17 QIDS-SR-16*</td>
<td>11</td>
<td>Medications Combined</td>
<td>33 (28.2)*</td>
<td>39 (33.3)</td>
<td>39 (33.3)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65</td>
<td>CIT + CBT</td>
<td>23 (35.4)*</td>
<td>15 (23.1)</td>
<td>20 (30.8)*</td>
<td></td>
</tr>
</tbody>
</table>

BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; CM = clomipramine; DES = desipramine; FLX = fluoxetine; HAMD = Hamilton Depression Rating Scale; ME = mecamyline hydrochloride; n = sample size; p = Probability; PBO = placebo; PI = pindolol; SSRI = selective serotonin reuptake inhibitors; QIDS-SR16 = Quick Inventory of Depressive Symptoms Self Report (16); TE = testosterone; VEN = venlafaxine

*aThe QIDS-SR reported outcomes.

*aNote that response was defined as 50 percent change relative to baseline unless noted within the table.

bRemission was defined as the standard threshold value for the particular instrument.
**Figure 12. Forest plots of the combined versus combined therapies for the outcome of response**

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add NonSSRI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura 2008[^2,^3] (SSRI+CIT vs. SSRI+CM, H-21)</td>
<td>1.22 (0.68, 2.21)</td>
<td>11/18 9/18</td>
</tr>
<tr>
<td>*Rush 2006[^4]/Trivedi 2006[^11] (CIT+BUS vs. CIT+BUP, Q-16)</td>
<td>1.17 (0.91, 1.52)</td>
<td>88/279 77/286</td>
</tr>
<tr>
<td><strong>Add Augmenting Agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinan 1993[^2b] (SER+L1 vs. SER+L2, H)</td>
<td>0.90 (0.36, 2.24)</td>
<td>3/5 4/6</td>
</tr>
<tr>
<td>Dunner 2007[^9] (SER+ZL6 vs. SER_ZL8, M)</td>
<td>0.37 (0.08, 1.61)</td>
<td>2/19 6/21</td>
</tr>
<tr>
<td>Fava 2002[^11b] (FLX+DES vs. FLX+LI, H-17)</td>
<td>0.80 (0.36, 1.78)</td>
<td>8/34 10/34</td>
</tr>
<tr>
<td>Fava 1994[^9b] (FLX+DES vs. FLX+LI, H-17)</td>
<td>1.14 (0.32, 4.12)</td>
<td>4/14 3/12</td>
</tr>
<tr>
<td><strong>Add NonPharmacological Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Rush 2006[^4]/Trivedi 2006[^11] (CIT+BUS vs. CIT+CBT, Q-16)</td>
<td>1.31 (0.90, 1.92)</td>
<td>23/65 77/286</td>
</tr>
<tr>
<td>*Rush 2006[^4]/Trivedi 2006[^11] (CIT+BUP vs. CIT+CBT, Q-16)</td>
<td>1.12 (0.77, 1.63)</td>
<td>23/65 88/279</td>
</tr>
<tr>
<td>*Rush 2006[^4]/Trivedi 2006[^11] (Med vs. CIT+CBT, Q-16)</td>
<td>1.25 (0.81, 1.94)</td>
<td>23/65 33/117</td>
</tr>
</tbody>
</table>

BUP = bupropion; BUS = buspirone; CBT = cognitive behavioral therapy; CIT = citalopram; CM = clomipramine; Med = medication; DES = desipramine; FLX = fluoxetine; H = Hamilton Depression Rating Scale; H-17 = Hamilton Depression Rating Scale – 17 item; H-21 = Hamilton Depression Rating Scale – 21 item; LI = lithium; M = Montgomery-Asberg Depression Rating Scale (MADRS); Q-16 = Quick Inventory of Depressive Symptoms Self Report (16); SER = sertraline; SSRI = selective serotonin reuptake inhibitors

* Represent STAR*D studies.
Figure 13. Forest plot of combined versus combined therapies for the outcome of remission

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>No. of events</th>
<th>Combined Therapy 1</th>
<th>Combined Therapy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Add NonSSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUS vs. CIT+BUP, H-17)</td>
<td>0.99 (0.77, 1.27)</td>
<td>83/279</td>
<td>86/286</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUS vs. CIT+BUP, Q-16)</td>
<td>1.18 (0.94, 1.47)</td>
<td>108/279</td>
<td>94/286</td>
<td></td>
</tr>
<tr>
<td><strong>Add NonPharmacological Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUS vs. CIT+CBT, H-17)</td>
<td>0.77 (0.48, 1.24)</td>
<td>15/65</td>
<td>86/286</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUS vs. CIT+CBT, Q-16)</td>
<td>0.94 (0.63, 1.40)</td>
<td>20/65</td>
<td>94/286</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUP vs. CIT+CBT, H-17)</td>
<td>0.78 (0.48, 1.25)</td>
<td>15/65</td>
<td>83/279</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (CIT+BUP vs. CIT+CBT, Q-16)</td>
<td>0.79 (0.54, 1.18)</td>
<td>20/65</td>
<td>108/279</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (Med vs. CIT+CBT, H-17)</td>
<td>0.69 (0.41, 1.16)</td>
<td>15/65</td>
<td>39/117</td>
<td></td>
</tr>
<tr>
<td><em>Rush 2006</em>[^4^]/<em>Trivedi 2006</em>[^11^][^3^] (Med vs. CIT+CBT, Q-16)</td>
<td>0.92 (0.59, 1.44)</td>
<td>20/65</td>
<td>39/117</td>
<td></td>
</tr>
</tbody>
</table>

BUP = bupropion; BUS = buspirone; CBT = cognitive behavioral therapy; CIT = citalopram; H-17 = Hamilton Depression Rating Scale – 17 item; Med = medication; Q-16 = Quick Inventory of Depressive Symptoms Self Report (16)

*Represent STAR*D studies.
Interventions in Patients With Subsyndromal Depression or Dysthymia

Overview of Study PICOT Characteristics: Subsyndromal Depression

Population
A single study evaluated patients described as those “with residual symptoms of a depressive disorder” and characterized by a score greater than seven but less than 10 on the HAMD-21 items. These subjects were classified as having subsyndromal depression following an acute episode. Seventy percent of the subjects were women and ethnicity was not reported. Mean age was 39 years.

Inadequate Response
There were no specific criteria reported for previous failure to paroxetine other than having residual symptoms and having been treated for 42 to 300 days.

Mental Health History
Failure of response to paroxetine was determined prospectively over a 4-week period. The subjects’ failure to respond to the current treatments were retrospective but the manner of determining this was not reported. Similarly, the history of any previous inadequate responses to treatment or length of the current episode was not reported.

Intervention and Comparators
In this study, subjects who had residual symptoms while on paroxetine were randomized to a continuation of paroxetine (20 to 40mg/d) or switched to mirtazapine (15 to 30mg/day) for an average of 36 days.

Outcomes
The primary outcomes in this study were rated on the HAMD-21. Changes in metabolic rate values and changes in the Arizona Sexual Experience Scale (ASEX) score showed no differences between groups.

Setting
This study was conducted in the Czech Republic and the setting from which patients were recruited was not reported.

Risk of Bias: Subsyndromal Depression
In this study, the type of randomization process and the degree of compliance was not clearly reported; all other categories were acceptable.

Efficacy of Treatment: Subsyndromal Depression
The findings of this study do not report differences between groups; rather, it is reported that 70 percent of subjects had a positive effect on residual symptoms but no mean change scores.
were given. Differences between groups were shown on the ASEX Scale in favor of mirtazapine starting from the first week of treatment \( (p = 0.004) \).

**Overview of Study PICOT Characteristics: Dysthymia**

**Population**

One study\(^{117} \) evaluated subjects with dysthymia as diagnosed by the DSM-IV structured clinical interview and with a score of 12 or more on the HAMD-21 scale. Subjects with MDD or other types of depression (e.g., partial remission from depression) were excluded. Sixty-eight percent of the sample were women and the mean age was 42 years. Ethnicity was not reported.

**Inadequate Response**

Subjects were not excluded because of failures (other than the current response to paroxetine). The number of previous episodes of failure to treatment was not reported, but the mean duration of the depression was approximately 12 years with an onset at approximately 29 years of age.

**Mental Health History**

The subjects’ failure to the current treatment was retrospective but the manner of determining this was not reported. Similarly, the history of any previous inadequate responses to treatment or length of the current episode was not reported.

**Intervention and Comparators**

Subjects were randomized to either paroxetine (40mg/d) or paroxetine (20mg/d) and amisulpride (50mg/d).

**Outcomes**

The primary outcome for the study was response (defined as 50 percent change from baseline) for the HAMD (type not specified) and a score of one or two on the CGI-2. Remission was a secondary outcome and was not explicitly defined, but was assumed to be defined as a score on the HAMD.

**Setting**

The study was conducted in Italy and subjects were recruited from outpatient settings.

**Risk of Bias: Dysthymia**

This paper was at low risk of bias and there was only uncertainty around the role of the study sponsor.

**Efficacy of Treatment in Dysthymia**

Fifty-four percent of subjects on paroxetine alone and 56 percent in the combined group achieved response (50 percent change) on the HAMD-NS. Remission was defined as a score of seven or less and those achieving remission were 32 percent for paroxetine alone and 44 percent for the combination treatment group. Neither response nor remission was shown to be statistically different between the treatment groups.
Adolescents

Overview of Study PICOT Characteristics: Adolescents

There were three studies (13 publications) evaluating adolescents who had not responded to previous SSRI treatment, and from these one trial could not have data extracted. This study did have “Phase II” subjects (those who had an inadequate response) and two of the three study arms were eligible for this review (medication or CBT). Proportions of subjects who reached this stage were reported and contact with the authors confirmed that data are not currently available for Phase II subjects. The two other trials evaluated dose escalation of fluoxetine or switch to other antidepressants with and without the addition of CBT.

Population

Two studies evaluated children or adolescents with MDD. In the dose escalation study the eligibility criteria included children (aged 8 to 12 years) and adolescents (age 13 to 18 years). The mean age was 12 and 14 in the two groups respectively, but there were significantly more children (less than 13 years old) in the lower dose group. The majority (60 percent) were males and of Caucasian ethnicity (87 to 93 percent). In the Treatment for Resistant Depression in Adolescents (TORDIA) study, the majority of the sample (68 to 72 percent) were female adolescents from age 12 to 18; the average age was 16 years (SD 1.6) and predominately (>80 percent) of white race.

Inadequate Response

In the TORDIA trial, subjects who were currently taking an SSRI were established retrospectively. In this trial, subjects who had previously failed two or more adequate trials of an SSRI, who had a history of nonresponse to venlafaxine, or nonresponse to CBT (≤7 sessions), were excluded. Potential participants who were receiving CBT or were on other medications with psychoactive properties were also excluded. Inadequate response was defined as less than 30 percent change on the Children’s Depression Rating Scale–Revised (CDRS-R) for those who still had a score greater than or equal to 40 on this scale, and were in treatment on an SSRI for a minimum of 8 weeks. In the dose escalation study, inadequate response was similarly defined as a CDRS-R score with less than a 30 percent change after 8 weeks at the base dose of 20mg/d.

Mental Health History

The dose escalation study did not provide details of the previous mental health history; eligibility for this trial required moderate severity (CDRS-R score greater than 40) and a CGI of at least four. In the TORDIA trial, mean CDRS-R scores at baseline varied from 58 to 60 (19 to 22 on the Beck Depression Inventory– BDI) and CGI scores from 4.4 to 4.5. Approximately 74 percent of participants were in a first episode of depression; the mean duration of the current episode varied from 21 to 24 months. Approximately 25 percent of participants had a history of suicide attempts (varying from 21 to 27 percent). The level of comorbidity was significant in this group and approximated 36 percent for anxiety disorder and post-traumatic stress disorder (21 to 24 percent post-traumatic stress disorder alone), 14 to 18 percent for attention deficit hyperactivity disorder, and 27 to 32 percent for dysthymia. However, there were no differences in rates of comorbidity between the four treatment groups.
**Intervention and Comparators**

The initial dose of 20mg/d of fluoxetine was increased to 40mg/d in the dose-escalated group; this could be increased to 60mg/d after 4 weeks. The length of treatment was 10 weeks. In the TORDIA trial, study subjects were randomized to four treatment arms that included venlafaxine alone (up to 150mg/d), venlafaxine combined with CBT, citalopram, fluoxetine, or paroxetine (up to 40mg/d for all SSRIs) alone, or with CBT. CBT consisted of up to 12 (60 to 90 minute) sessions and one quarter to one half consisted of sessions with the family. The reported mean number of sessions was 8.3 across treatment groups. Subjects were tapered off the initial SSRI. All participants received family psychoeducation which consisted of providing information about depression, adverse events, and coping with mood disorders. The treatment interval was 12 weeks. After 12 weeks of treatment, responders could continue in their assigned treatment arm, and no-responders received open-label treatment for an additional 12 weeks (24 weeks total). Open treatment was not controlled and could result in a switch to a new antidepressant, dose increase (for those not at the maximum dose), augmentation, or the addition of CBT or other psychotherapy.

**Outcome**

Both studies had two primary outcomes based on “adequate clinical response” defined as a score of two or less on the CGI Improvement subscale and a 50 percent improvement on the CDRS-R.

**Setting**

These studies were conducted in the United States and subjects were recruited from clinical sources and public advertisements (newspapers and radio) for both studies.

**Risk of Bias in Studies With Adolescents**

The dose escalation trial was generally well conducted, but the two treatment groups had some differences at baseline, even though the mean age was similar. Additionally, the primary author is employed by the study sponsor. The TORDIA trial had some potential threats to validity with regards to the method of allocation, concealment and blinding of the outcome assessor; there was low risk of bias in all other aspects of the study. A washout period for subjects on an SSRI other than fluoxetine was undertaken for 2 weeks prior to switching to the new intervention. The method of assessing compliance with the treatment was not reported, but the proportion of subjects who did not comply was reported. Overall, the TORDIA trial had a low risk of bias.

In the TORDIA trial, treatment fidelity for the CBT was well detailed and approximately 94 percent of reviewed tapes were found to be acceptable by on-site supervisors and by an external consultant.

**Efficacy of Treatment in Adolescents**

**Response and Remission**

In the dose escalation study, response was achieved by 5 of 15 and 10 of 14 subjects in the low- and high-dose groups respectively; the study was not powered to detect differences between groups although the investigators noted that there were no statistically significant differences...
between the groups. Similarly, there were no significant differences between groups when considering mean CGI improvement scores.

Table 16 details the study findings for the TORDIA trial findings at 12 weeks.\textsuperscript{144,145,147,148} There were no statistically significant differences between the medication alone groups. There was a statistically significant difference between the CBT groups in favor of including CBT for all outcomes. The main effect of CBT was consistent even after controlling for baseline severity factors (BDI scores and post-traumatic stress).

At the 24-week followup, adolescents within the TORDIA trial showed continued improvement.\textsuperscript{146,149} After 12 weeks of treatment, responders could continue in their assigned treatment arm, and nonresponders received open-label treatment for an additional 12 weeks (24 weeks total). Open treatment was not controlled and could result in a switch to a new antidepressant, dose increase (for those not at the maximum dose), augmentation, or the addition of CBT or other psychotherapy. From the original sample (n=334) only 78.1 percent (n=261) were assessed at 24 weeks. The findings at 24 weeks suggest that the likelihood of remission was higher and time to remission was faster for those who showed clinical response at 12 weeks, relative to those who did not show response by 12 weeks (61.6 percent versus 18.3 percent).\textsuperscript{146} Among all participants, failure to achieve remission at week 24 was associated with higher baseline depression, hopelessness, anxiety, and family conflict.\textsuperscript{146}

Table 16. Results from TORDIA trial for ITT sample at 12 weeks

<table>
<thead>
<tr>
<th>ITT Sample</th>
<th>SSRI (n=168)</th>
<th>Venlafaxine (n=166)</th>
<th>No CBT (n=168)</th>
<th>CBT (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (%)</td>
<td>79 (47.0)</td>
<td>80 (40.5)</td>
<td>68 (40.5)</td>
<td>91 (54.8)</td>
</tr>
<tr>
<td>CGI-I ≤2 (%)</td>
<td>86 (51.2)</td>
<td>92 (55.4)</td>
<td>80 (47.6)</td>
<td>98 (59.0)</td>
</tr>
<tr>
<td>Change CDRS-R ≥50 (%)</td>
<td>86 (51.8)</td>
<td>86 (51.8)</td>
<td>79 (47.0)</td>
<td>191 (60.8)</td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy; CDRS-R = Children’s Depression Rating Scale- Revised; CGI-I = Clinical Global Impression – Improvement scale; ITT = intention to treat analysis; SSRI = selective serotonin reuptake inhibitors
*Response defined as “adequate clinical response” on the CGI-I.

Other Outcomes

Using the Children’s Global Adjustment Scale, functional status was assessed in the TORDIA trial and no main effects or interactions were shown. For responders at week 12, 19.6 percent relapsed at 24 weeks; predictors of relapse were similar to those for lack of eventual remission and included higher baseline depression (via interview and self-report), poorer functioning, and presence of dysthymia.\textsuperscript{146} A cost-effectiveness analysis was undertaken at 24 weeks within the TORDIA trial.\textsuperscript{149} The analysis would suggest that adolescents receiving CBT with medication achieved 8.3 more depression free days, and 11 more depression improved days across 24 weeks of treatment. However, combination therapy was significantly more expensive than medication switch alone.\textsuperscript{149}

Strength of Evidence Ratings

Adults With MDD

We applied the criteria for grading the strength of evidence (SOE) to the studies and found that all studies directly evaluated the outcomes of remission and response and, as such, were not deficient in this domain. There was some variation in consistency of the effect depending on the
treatment strategy. In general, most studies had relatively few participants, and when studies were considered as a group, there was difficulty in demonstrating a clinically useful conclusion. Studies were not designed to establish equivalence, noninferiority, or superiority. The majority of the studies showed no differences between treatment groups, suggesting uncertainty about these differences. Even when studies were sufficiently powered for the primary outcome, a statistically significant difference between groups was rarely found, making clinical interpretation difficult with respect to selection of an optimal strategy relative to the standard or usual treatment.

The outcomes of harms are detailed in KQ2. When we evaluated the SOE of the studies that reported the harms of suicidality, weight gain, and sexual dysfunction, all treatment strategies in KQ1 were consistently rated as insufficient. Overall, we found few studies that reported on the harms of interest. The inability to distinguish if the studies measured these harms, or simply did not report them (either because no events occurred or they occurred at the lowest frequencies), made rating SOE problematic. We considered the measurement of these critical and important harms to be necessary for all studies given the potential of these serious adverse events in MDD and with most treatment approaches.

There were several issues with regard to applicability of the eligible studies. Overall, the studies were comprised of adult subjects that were not representative of the broader population who experience MDD and who might experience a failed response to an SSRI. Subjects were predominately white women between the ages of 40 to 50, and who had had more than one previous failure to treatment. For combined therapies, there was some concern about the dose and augmenting agent selection and the likely use of many of these in the context of primary care.

**Monotherapy Versus Monotherapy in MDD**

The grading of SOE for adults with MDD who have failed to respond to an SSRI is shown in Table 17. With respect to monotherapy compared with monotherapy interventions, we grouped all treatment approaches together, given the small number of studies and the various drugs and CBT. There were several important study limitations, in particular the lack of adequate randomization and the sample sizes of the studies. The confidence intervals were generally small and the effect sizes of similar magnitude were rated as consistent. All statistical testing undertaken in these studies showed no significant differences between groups, suggesting no advantage of any one monotherapy over another. None of the studies in this grouping explicitly stated that the trials were designed for establishing superiority. Overall, however, our rating of the SOE for all monotherapy strategies (dose escalation, switching to another antidepressant, or psychological intervention) was low. This suggests that future research would likely affect the estimates of effect sizes established in these studies.

**Monotherapy Versus Combined Therapies in MDD**

The SOE ratings for the studies comparing monotherapies to combined therapies is detailed in Tables 18 to 26. We considered these augmenting studies both as a single group (Table 18) and as subgroups related to the number of studies evaluating specific agents. There were four subgroups we considered with respect to specific classes of agents and these included: atypical antipsychotics, individual agents (e.g., buspirone, lithium, mianserin), and then all other agents were categorized as a single group for SOE rating.
When we considered all studies with augmenting agents (12 different types) as a single group, we rated the studies evaluating monotherapies relative to adding augmenting agents as insufficient SOE. The degree of similarity for the effect sizes was rated as inconsistent, despite the fact that almost all agents showed no relative difference relative to the monotherapy; the estimates tended to have wide confidence intervals and were not consistently overlapping. The large number of treatment agents, differing treatment intervals, population characteristics, and the wide range of sample sizes contributed to this grading of insufficient (Table 18).

When considering atypical antipsychotic medications alone, a SOE rating of low for the outcome of response and remission was given88,95,108,122 (Table 19). There was a consistent effect favoring combined treatment with atypical antipsychotics. One study with a small sample size showed very large confidence intervals122 for the outcome of response. Two studies95,108 showed larger confidence intervals for remission and this may be related to the “subgroup” data specific to the failed SSRI group that we requested from the study authors. The original study data included larger sample sizes as subjects with failed response to nonSSRI medications were included. For this reason, we rated these four studies as having consistency in showing the same direction of effect (favoring combined therapy), but as imprecise because of the nonoverlapping confidence intervals (as well as a small sample size in a single study and “some” studies).

The studies that used buspirone as the augmenting agent were separated into those that switched to a different antidepressant monotherapy (Table 20) versus those that added buspirone to the current SSRI (to which subjects had an inadequate response) (Table 21). The SOE was graded as insufficient for the latter category, as the studies were deemed to have a greater number of study limitations relative to the STAR*D trial44,113 that evaluated switching to new monotherapies. The STAR*D trial showed no difference when adding buspirone relative to the different monotherapies after switching to a new antidepressant.

The remaining groupings for augmenting agents for lithium (Table 22), mianserin (Table 23), and “other agents” combined (Table 24) were all graded as insufficient SOE due to the small sample sizes and significant study limitations. It is difficult to determine any level of confidence in the effects of these agents despite the fact that none were shown to be any different relative to the comparator monotherapy.

We grouped all studies that maintained the current SSRI and then compared this treatment arm with one where a different SSRI, nonSSRI, or nonpharmacological treatment was added (Table 25). This group of studies was rated as low for the outcome of response because of the differing agents and the small sample sizes. For the outcome of remission, a grading of insufficient was given, as the study limitations were significant. There were two studies that compared switching from the current SSRI to a new monotherapy treatment and then compared this with the new agent combined with any other drug. The studies that evaluated switching to a new antidepressant and then adding aripiprazole would have been included in this group, had we been able to acquire the rates of response and remission for the SSRI failed group. For the two studies that did provide these outcomes, one study112 had wide confidence intervals and effect size because of the small sample size; the other study was the STAR*D cohort and had multiple treatment arms and comparisons. The evidence is graded as low and the findings suggest no relative advantage to switching to a new drug or CBT relative to adding buspirone or bupropion (Table 26).
Combined Therapy Versus Combined Therapy in MDD

A rating of insufficient for the SOE was given to the studies that compared combined therapies relative to other combined therapies (Table 27). The STAR*D study was the single study in this group reporting the outcome of remission. The studies comparing combinations relative to other combinations were consistent in that the relative risks were generally of the same magnitude and the effect sizes showed that no one combined therapy was different than any other, given the study limitations.
Table 17. SOE: Monotherapy versus monotherapy (pharmacological and nonpharmacological)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Outcome Response</td>
<td></td>
</tr>
<tr>
<td>10^14,88,90,103,104,106,110,112,115,119,121,122</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome Remission</td>
<td></td>
</tr>
<tr>
<td>8^44,88,90,103,104,106,110,115,119,121</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Suicidality</td>
<td></td>
</tr>
<tr>
<td>2^44,103,106,113</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Weight Gain</td>
<td></td>
</tr>
<tr>
<td>2^88,103,106,119,121</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Sexual Dysfunction</td>
<td></td>
</tr>
<tr>
<td>2^90,103,106</td>
<td>RCT/CCT</td>
</tr>
</tbody>
</table>

A/E = adverse event; CCT = clinical controlled trial; N/A = not applicable; No. = number; NR = not reported; RCT = randomized controlled trial; RR = relative risk
Table 18. Monotherapy versus combined therapy (maintaining SSRI or switching AD versus adding any augmenting pharmacological agents)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Combined Therapy</th>
<th>Mono-therapy</th>
<th>RR or (% A/E)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>184,80,84,86,88,89,93,98,108,112-114,118-122,124</td>
<td>RCT/ CCT</td>
<td>Study limitations</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Diverse augmenting agents (n=12) Applicability issues with population, interventions, and comparators</td>
<td>1137</td>
<td>1904</td>
<td>RR range 0.40 to 13.0</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
<tr>
<td>44,87,88,95,101,108,112-114,119,132</td>
<td>RCT/CCT</td>
<td>Study limitations</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Diverse augmenting agents (n=7) Applicability issues with population, interventions, and comparators</td>
<td>1679</td>
<td>951</td>
<td>RR range 0.72 to 4.7</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
<tr>
<td>44,89,113</td>
<td>RCT/CCT</td>
<td>Study Limitations</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td>Diverse augmenting agents</td>
<td>N/A</td>
<td>N/A</td>
<td>% range (0.83 to 1.4)</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
<tr>
<td>88,119,121</td>
<td>RCT/CCT</td>
<td>Study Limitations</td>
<td></td>
<td></td>
<td></td>
<td>Diverse augmenting agents</td>
<td>N/A</td>
<td>N/A</td>
<td>% range (0.0 to 39.7)</td>
<td>Insufficient</td>
<td>Important</td>
</tr>
<tr>
<td>84</td>
<td>RCT</td>
<td>Study Limitations</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>% range (10 to 45)</td>
<td>Insufficient</td>
<td>Important</td>
</tr>
</tbody>
</table>

AD = antidepressant; A/E = adverse event; CCT = clinical controlled trial; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk.
### Table 19. Monotherapy versus combined therapy (maintaining SSRI and adding or switching atypical antipsychotics agents)*

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<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
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<tr>
<td>Combined Therapy</td>
<td>Mono-therapy</td>
<td>RR or (% A/E)</td>
<td></td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>RCT</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
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<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Combined Therapy</td>
</tr>
<tr>
<td>RCT</td>
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<tr>
<td>290</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Outcome Remission</th>
</tr>
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<tbody>
<tr>
<td>No. of Patients</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>Combined Therapy</td>
</tr>
<tr>
<td>RCT</td>
</tr>
<tr>
<td>327</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome Suicidality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Combined Therapy</td>
</tr>
<tr>
<td>RCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Combined Therapy</td>
</tr>
<tr>
<td>RCT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Sexual Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Combined Therapy</td>
</tr>
<tr>
<td>RCT</td>
</tr>
</tbody>
</table>

*A/E = adverse event; N/A = not applicable; No. = number; RCT = Randomized controlled trial; RR = relative risk

*Two studies had some proportion of the enrolled subjects that had failed to an SSRI alone. Request for stratified information was not provided for adverse events. Abbreviations:
Table 20. Monotherapy versus combined therapy (switching AD and adding Buspirone)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
</tr>
<tr>
<td></td>
<td>Combined Therapy</td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design</td>
</tr>
<tr>
<td>AD = antidepressant; A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; STAR*D = sequenced treatment alternatives to relieve depression</td>
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</tr>
</tbody>
</table>

**Outcome Response**

<table>
<thead>
<tr>
<th>Study</th>
<th>Consistent</th>
<th>Direct</th>
<th>Imprecise</th>
<th>STAR*D</th>
<th>No.</th>
<th>RR range</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>STAR*D</td>
<td>286</td>
<td>0.96 to 1.02</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
</tbody>
</table>

**Outcome Remission**

<table>
<thead>
<tr>
<th>Study</th>
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<th>Direct</th>
<th>Imprecise</th>
<th>STAR*D</th>
<th>No.</th>
<th>RR range</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>STAR*D</td>
<td>286</td>
<td>1.21 to 1.70</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
</tbody>
</table>

**Outcome of Suicidality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Consistent</th>
<th>Direct</th>
<th>Imprecise</th>
<th>STAR*D</th>
<th>No.</th>
<th>% range</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>(0.83 to 1.4)</td>
<td>Insufficient</td>
<td>Critical</td>
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</table>

**Outcome of Weight Gain**

<table>
<thead>
<tr>
<th>Study</th>
<th>Consistent</th>
<th>Direct</th>
<th>Imprecise</th>
<th>STAR*D</th>
<th>No.</th>
<th>% range</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>1.21 to 1.70</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
</tbody>
</table>

**Outcome of Sexual Dysfunction**

<table>
<thead>
<tr>
<th>Study</th>
<th>Consistent</th>
<th>Direct</th>
<th>Imprecise</th>
<th>STAR*D</th>
<th>No.</th>
<th>% range</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>(0.83 to 1.4)</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
</tbody>
</table>
Table 21. Monotherapy versus combined therapy (maintaining SSRI and adding Buspirone)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Combined Therapy</th>
<th>Mono-therapy</th>
<th>RR or (% A/E)</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCT/CCT</td>
<td>Study Limitations</td>
<td>Consistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td></td>
<td></td>
<td>RR range 1.06 to 1.09</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
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<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td>From 2 studies none reported outcome</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td>From 2 studies none reported outcome</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td>From 2 studies none reported outcome</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
<td>Critical</td>
</tr>
</tbody>
</table>

A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors
Table 22. Monotherapy versus combined therapy (maintaining SSRI and adding Lithium agents)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
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<th>No. of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined Therapy</td>
<td>Mono-therapy</td>
<td>RR or (%) A/E</td>
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</tr>
<tr>
<td><strong>Outcome Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (^{68,112,118,124})</td>
<td>RCT</td>
<td>Study Limitations</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>67</td>
<td>81</td>
<td>RR range 0.40 to 4.20</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Outcome Remission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (^{112})</td>
<td>RCT</td>
<td>Study Limitations</td>
<td>N/A</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>9</td>
<td>32</td>
<td>N/A</td>
<td>Insufficient</td>
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<tr>
<td><strong>Outcome of Suicidality</strong></td>
<td></td>
<td></td>
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<td></td>
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<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Outcome of Weight Gain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Outcome of Sexual Dysfunction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors
Table 23. Monotherapy versus combined therapy (maintaining SSRI and adding Mianserin agents)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Quality</th>
<th>Effect</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of Patients</td>
<td>RR or (% A/E)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined Therapy</td>
<td>Mono-therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR range</td>
<td>0.97 to 1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR range</td>
<td>1.17 to 1.54</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>% range</td>
<td>(2.0 to 15.8)</td>
</tr>
</tbody>
</table>

Outcome Response

| Outcome Remission
| Outcome of Suicidality
| Outcome of Weight Gain
| Outcome of Sexual Dysfunction

A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors
Table 24. Monotherapy versus combined therapy (maintaining SSRI and adding other augmenting agents)

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of Patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR or (% A/E)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Importance</td>
</tr>
</tbody>
</table>

**Outcome Response**

| 6,80,84,86,89,93,114 | RCT | Study Limitations | Inconsistent | Indirect | Imprecise |                      | 235 | 227 | 0.23 to 4.55 | Insufficient | Critical |

**Outcome Remission**

| 2,87,101,114,132 | RCT | Study Limitations | Consistent | Indirect | Imprecise |                      | 230 | 227 | 1.06 to 1.20 | Insufficient | Critical |

**Outcome of Suicidality**

| 1,89 | RCT | Study Limitations | N/A | Direct | N/A | N/A | N/A | % range (10 to 45) | Insufficient | Important |

**Outcome of Weight Gain**

| 0 | N/A | N/A | N/A | Direct | N/A | N/A | N/A | N/A | Insufficient | Important |

**Outcome of Sexual Dysfunction**

| 1,84 | RCT | Study Limitations | N/A | Direct | N/A | N/A | N/A | N/A | % range (10 to 45) | Insufficient | Important |

A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors
Table 25. Monotherapy versus combined therapy (maintaining SSRI and adding another treatment, nonSSRI, SSRI and nonpharmacological)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>Effect</td>
</tr>
<tr>
<td>Combined Therapy</td>
<td>Monotherapy</td>
</tr>
</tbody>
</table>

**Outcome Response**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Studies</th>
<th>RR range</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4,62,83,94,98,118</td>
<td>RCT</td>
<td>Study limitations</td>
<td>Inconsistent</td>
<td>Direct</td>
<td>Imprecise</td>
<td>Diverse interventions Issues with applicability</td>
<td>74</td>
<td>0.47 to 19.00</td>
<td>Insufficient</td>
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</table>

**Outcome Remission**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Studies</th>
<th>RR or (%) A/E</th>
<th>Importance</th>
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</thead>
<tbody>
<tr>
<td>1128</td>
<td>RCT</td>
<td>Study limitations</td>
<td>N/A</td>
<td>Direct</td>
<td>Imprecise</td>
<td></td>
<td>20</td>
<td>1.20 [CI 0.61 to 2.34]</td>
<td>Insufficient</td>
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</tbody>
</table>

**Outcome of Suicidality**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Studies</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Insufficient</td>
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</table>

**Outcome of Weight Gain**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Studies</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

**Outcome of Sexual Dysfunction**

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>No. of Studies</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Direct</td>
<td>N/A</td>
<td></td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

A/E = adverse event; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors
Table 26. Monotherapy versus combined therapy (switching monotherapy versus adding another treatment, nonSSRI, SSRI, and nonpharmacological)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>No. of Patients</td>
</tr>
<tr>
<td><strong>Outcome Response</strong></td>
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</tr>
<tr>
<td>2 RCT/ CCT</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Outcome of Remission</strong></td>
<td></td>
</tr>
<tr>
<td>1 RCT/CCT</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Outcome of Suicidality</strong></td>
<td></td>
</tr>
<tr>
<td>1 RCT/CCT</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Outcome of Weight Gain</strong></td>
<td></td>
</tr>
<tr>
<td>0 N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Outcome of Sexual Dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>0 N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

A/E = adverse event; CCT = controlled clinical trial; N/A = not applicable; No. = number; RCT = randomized controlled trial; RR = relative risk; SSRI = selective serotonin reuptake inhibitors; STAR*D = sequenced treatment alternatives to relieve depression
### Table 27. Combined therapy versus combined therapy (pharmacological and nonpharmacological)

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
</tr>
<tr>
<td>No. of Studies</td>
<td>Design</td>
</tr>
<tr>
<td>6</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome Response</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome Remission</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Suicidality</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Weight Gain</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>RCT/CCT</td>
</tr>
<tr>
<td>Outcome of Sexual Dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

A/E = adverse event; CCT = clinical controlled trial; N/A = not applicable; No. = number; NR = not reported; RCT = randomized controlled trial; RR = relative risk
Adults With Dysthymia and Subsyndromal Depression

The studies evaluating these populations were each limited to a single trial. One study with patients with subsyndromal depression\textsuperscript{129} had significant risk of bias and poor reporting; as such we rate this as insufficient SOE. The study on dysthymia\textsuperscript{117} had low risk of bias, but had a very small sample size, and the study subjects were predominately middle aged white females. For this reason we have judged this study as insufficient SOE.

Adolescents

From two studies reporting outcomes on children and adolescents, one was a pilot study evaluating dose escalation\textsuperscript{138}. The TORDIA trial\textsuperscript{42,141,144-149} evaluating efficacy of monotherapy relative to combined therapy was at low risk of bias and evaluated and reported harms well. Study findings showed no significant differences between groups. Although the intent of the trial was specified as establishing the superiority of the venlaxafine monotherapy arm, the margins of superiority and the statistical analysis for this were not reported. The SOE was judged as a low grade.

KQ2. What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

Key Messages

Harms for interventions used in both adults and adolescents with MDD that had failed to respond to an SSRI were predominantly derived from RCTs that evaluated treatment strategies in this population; no observational studies were eligible. A clear trend for harms was difficult to specify across the differing interventions in adults. Harms were well evaluated in the one study of adolescents and a pilot dose escalation study.

Reporting and collecting of harms was problematic, particularly for predefining harms including serious and severe events, and reporting the total number of events per group in the studies with adults. The studies evaluating harms in adolescents provided high quality evidence for harms within this population when receiving pharmacological and psychological treatment.

Severe events and serious events (including suicidality) were inconsistently reported in studies with adult MDD populations.

A limited number of studies undertook statistical evaluation comparing harms between groups.

Harms in Adults With MDD, Dysthymia, and Subsyndromal Depression

From the 41 studies evaluating adults, all but one study included subjects with MDD; two studies evaluated subjects with subsyndromal depression\textsuperscript{129} and dysthymia\textsuperscript{117}. As noted previously, five studies\textsuperscript{107,150,178-180} and seven STAR*D publications\textsuperscript{181-187} did not have data that could be extracted. No observational studies with the required patient population and evaluation of harms was eligible for this CER. The summary of harms thus reflects those reported within the eligible studies.
We present the harms evidence for the eligible and extracted studies based on the type of treatment comparisons as follows: (1) monotherapy compared with monotherapy; (2) monotherapy compared with combined therapy; and, (3) combined therapy compared with combined therapy. Some studies evaluated more than two treatment arms, and are included in multiple sections, dependent on the drugs used.

Description of Studies Reporting Harms in Adults With MDD

Monotherapy Versus Monotherapy in Adult MDD

In the six studies having at least one monotherapy treatment arm, all but one study\textsuperscript{112} reported some aspect of safety and tolerability. None of the studies were specifically designed to compare the effect of harms between different monotherapies. One study\textsuperscript{115} included a proportion of subjects who had failed to respond to an SSRI; following email contact with the author, stratified information for outcomes of benefit (not harm) were provided.

The method of assessing adverse events differed greatly among studies, with a limited number of studies using standardized methods or scales. Figure 14 shows the ratings on the McHarm scale for evaluating risk of bias and reporting within comparative studies. Forty percent of the studies indicated that the harms reported were those that were observed in 2 or 3 percent,\textsuperscript{103,106} 5 percent,\textsuperscript{85,119} or 10 percent of subjects;\textsuperscript{88,90} the remaining studies did not specify, or were unclear as to why the harms reported were included. None of the studies provided any a priori definitions of the harms, or of serious or severe events. Similarly, the mode of how harms were collected or the training of the person collecting them was not specified. Generally, the number of subjects who withdrew were specified per treatment arm; however, the number of specific adverse events per treatment arm were not well specified (50 percent).
Table 28 shows the rates of reported harms as a function of the treatment arm. Seven main categories of harms were selected to include within the summary table, but others were reported within the studies. The STAR*D cohort reported only the frequency of events as a range from one to 100 percent, not specifying the types of events as individual frequencies, and similarly identified numbers of serious events as having “at least” one event. One study explicitly identified that no serious events had occurred, and three studies (five publications) identified suicide events had explicitly not occurred; for the STAR*D, trials we assumed that serious psychiatric events encompassed suicidality. Rates of discontinuation due to adverse events were variable. In studies with open label prospective failure components, the number of patients who had adverse events and did not proceed to the next phase was not consistently reported. In studies with historical failure, the proportion of subjects who had experienced inadequacy due to intolerance because of harms was not detailed.

Two studies reported on both serious and suicide related events. Other adverse events not reported in Table 28 include dry mouth, dizziness, and fatigue. Increased appetite or weight gain was reported in two studies.

Four studies evaluated statistical differences in rates of harms, however, two of these primarily evaluated the comparisons for the monotherapy group relative to the combined therapy group. Another study evaluated differences between two methods of switching from an SSRI to duloxetine; no statistical differences were found between the two methods.
Table 29 details the reporting of harms in studies comparing monotherapies to combined therapies. One study\textsuperscript{112} reported harms when evaluating monotherapies relative to combined therapies. Only one study\textsuperscript{114} was designed to assess the effect of therapies for both efficacy and harms in patients who had excess sleepiness and fatigue despite previous adequate SSRI treatment. The subjects in this trial were partial responders for the current episode. This study included specific measures of sleepiness and fatigue as part of the primary outcomes.

The method of assessing adverse events differed greatly among studies, with a limited number of studies using standardized methods or the use of scales to assess harms. Figure 15 shows the ratings on the McHarm scale for evaluating risk of bias and reporting within comparative studies. Eleven studies (40 percent) indicated that the harms reported were those that were observed in two to three percent,\textsuperscript{108} five percent,\textsuperscript{79,87,101,105,109,114,119,126,131,132} or 10 percent of subjects;\textsuperscript{86,88,124} however, three of these studies did not report harms specific to the SSRI subgroup.\textsuperscript{79,105,108,109,126,131} The remaining studies did not specify why the harms reported were included or were unclear (20 percent). All but one study\textsuperscript{80} provided a priori definitions for serious harms. Similarly, definitions for predefining the harms or how these would be classified as severe were not detailed in any study (Figure 16). The mode of collecting harms was unclear or not identified in all but three studies,\textsuperscript{91-93,97,130} which collected reports of harms, or their training was rarely specified. Generally, the number of subjects who withdrew were specified per treatment arm, and the total number of adverse events was generally reported.
Fifteen of 29 studies indicated that some type of statistical comparison between groups had been undertaken; however, only five studies specified the type of analyses and the remaining ones did not. One study showed that weight gain, dry mouth, somnolence, peripheral edema, and hypersomnia differed between the combined fluoxetine and olanzapine group relative to the fluoxetine group; rates were higher in the combined group. In this same study no differences in rates of adverse events were shown between the combined group relative to olanzapine monotherapy. Another study evaluating olanzapine showed differences relative to baseline but not between treatment groups.

Another study evaluated differences between two monotherapy doses, or sertraline and sertraline combined with mianserin; statistical differences were shown only for the adverse event of sedation, with rates being higher in the combined therapy group. One study showed statistical differences in nausea and feeling jittery for the combined SSRI and modafinil group.

There were four studies that provided stratified outcomes of benefit for the SSRI subgroup alone. However, these studies did not provide stratified event rates for harms; as such, the rates of harms are not detailed as they reflect mixed antidepressant effect. For two studies the pooled analyses publication indicated that there were no differences between groups due to the antidepressant; this pooled analysis found that the combined therapy group with aripiprazole had approximately twice the incidence of adverse events (akathisia, restlessness, insomnia, fatigue, blurred vision, and constipation). The harms in another study were evaluated statistically and did not differ between antidepressants alone or combined with risperidone groups. Another study found rates of events to be similar between antidepressants.
versus antidepressants combined with risperidone, but differences were not evaluated statistically.

Other adverse events not reported in Table 30 include dry mouth,86-88,101,103,114,118,119,121,132 dizziness,79,86,96,105,109,114,126,131 and fatigue.79,82,83,88,105,109,121,126,131 Increased appetite was reported in two studies,87,88,101,132 and cardiovascular problems (hypotension, tachycardia, or bradycardia) were identified in five studies.80,82-84,96,114 For nonpharmacological therapies, most studies assumed that there were no adverse events to report with exercise,127 cognitive behavioral therapy,94 or dialectical behavior therapy.128

**Combined Therapies Versus Combined Therapies in Adult MDD**

From the six studies comparing combined therapies, none were designed to assess the effect of therapies on harms. The method of assessing adverse events differed greatly among studies with a limited number of studies using standardized methods or the use of scales to assess harms. Figure 16 shows the ratings on the McHarm scale for evaluating risk of bias specific to harms. A single study from the six specified that the harms reported represented those that were present in at least 10 percent of subjects.88 The remaining studies did not specify, or were unclear as to, why the harms reported were included (85 percent). No study predefined the harms, or the severe or serious harms. The mode of collecting harms, who collected the harms reports, or their training was generally not specified. Generally, the number of subjects who withdrew were specified per treatment arm, and the total number of adverse events were reported.

**Figure 16. Percent of studies evaluated using the criteria for risk of bias for adverse events using the McHarm scale for combined therapies alone.**
Table 30 shows the rates of reported harms as a function of the treatment arm. The STAR*D cohort reported only the frequency of events and did not specify the type of events or serious events. Two studies explicitly identified that serious events had occurred, or that suicide events had explicitly occurred. Rates of discontinuation due to adverse events were variable.

A single study reported evaluating statistical differences between groups. Other adverse events not reported in Table 30 include dry mouth, dizziness, and fatigue, and cardiovascular problems (hyper- and hypotension, tachycardia, or bradycardia) were identified in one study.

Description of Harms in Studies With Dysthymia and Subsyndromal Depression

One study evaluated patients with dysthymia and found no differences between treatment groups (paroxetine vs. paroxetine + amisulpride). The presence of galactorrhoea and menstrual disorders were noted in 18 and 9 percent of female patients, respectively. These adverse events were not observed in the paroxetine alone group. Other harms reported included low rates of gastrointestinal problems, sexual dysfunction, dry mouth and headache, and some sexual dysfunction. Consistent with studies already described, this study did not predefine harms, serious or severe, and indicated that harms were assessed through “spontaneous” notification (passive methods). Nor was the training of the person collecting harms specified or the frequency and timing of collection. This study did account for all study withdrawals and adequately reported the total number of adverse events and as a function of groups for each type of harm.

The single study evaluating harms in patients with subsyndromal depression (following an acute episode) primarily assessed safety and not efficacy. In addition, the study evaluated the relationship between adverse events and the corresponding metabolic status of the isoenzyme CYP 2D6; the rationale for this is that paroxetine is a potent inhibitor of this enzyme which may lead to increased adverse reactions. Adverse effects were measured using the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale and the ASEX Scale. The study showed no statistical difference in the UKU scale, and the ASEX scale showed an improvement from the first week of treatment in the mirtazapine group. Two subjects from the mirtazapine group discontinued due to problems with insomnia; no dropouts were reported for the paroxetine group.

Description of Harms in Studies With Adolescents

The TORDIA trial found no statistical differences between treatments with regard to the frequency of events, any serious adverse events (including suicide related symptoms), or dropouts related to adverse events at 12 weeks. Sleeping difficulty was the only psychiatric adverse event that occurred in greater than 5 percent of the subjects. Some harms showed a tendency for increased rates with the use of venlaxafine and these included skin rash and cardiovascular events; self-injury was also higher in those with higher suicidal ideation. Further analysis of suicidal adverse events showed that predictors of suicidal adverse events were linked with poor response to treatment at 12 weeks. The harms in the TORDIA study were collected using standardized instruments (4-item Kiddie Schedule of Affective Disorders and the Side Effects form for Children and Adolescents) and collected in an active manner. Reports of serious effects or worsening symptoms were reviewed weekly with the investigative team. Once any concerns for safety were raised, participants were monitored weekly. All
subjects completed the standardized safety scales at each pharmacological visit. The reporting of harms was clear, but severe harms were not defined a priori. Withdrawals were well described.

In the dose escalation study\textsuperscript{138} there were no statistically significant differences between the lower or higher dose groups with respect to solicited or unsolicited adverse events.

The dose escalation study\textsuperscript{138} used the Side-Effects Checklist and the reported harms were coded according to standardized terms. Description of serious events was not specified. Harms were assessed every two weeks.
Table 28. Summary of reported rates of harms for studies comparing monotherapy treatments

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>99</td>
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<td>9</td>
<td>VEN 150mg/d</td>
<td>NR</td>
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<td>VEN-ER 75-300mg/d</td>
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<td>9 (4.6)</td>
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<td>206</td>
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<td>NR</td>
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<td>15 (7.3)</td>
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<td>Rush44, 2006</td>
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<td>SER 50-200mg/d</td>
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<td>NR</td>
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<td>250</td>
<td>VEN 37.5-375mg/d</td>
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<td>NR</td>
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<td>5 (2)</td>
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</tr>
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<td>239</td>
<td>BUP 150-400mg/d</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>183</td>
<td>direct switch duloxetine 60-120mg/d</td>
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<td>8 (4.3)</td>
<td>33 (18)</td>
<td>13 (7.1)</td>
<td>2 (2.1)</td>
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<td>100 (54.6)</td>
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<td>2 (2.1)</td>
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<td>start-taper switch duloxetine 60-120mg/d</td>
<td>NR</td>
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<td>37 (20)</td>
<td>15 (8.2)</td>
<td>6 (3.2)</td>
<td>18 (9.7)</td>
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Table 28. Summary of reported rates of harms for studies comparing monotherapy treatments (continued)

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<tr>
<th>Study</th>
<th>Duration (weeks)</th>
<th>n*</th>
<th>Comparison and dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI problems n (%)</th>
<th>Sleep problems n (%)</th>
<th>Weight gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual dysfunction n (%)</th>
<th>Withdrawals due to A/E n (%)</th>
<th>Serious events n (%)</th>
<th>Suicide n (%)</th>
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<tbody>
<tr>
<td>Adding Augmenting Agent</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thase 2007</td>
<td>8</td>
<td>203</td>
<td>FLX 50mg/d</td>
<td>NR</td>
<td>(5.3)</td>
<td>NR</td>
<td>(2.4)</td>
<td>(6.8)</td>
<td>(19.4)</td>
<td>NR</td>
<td>NR</td>
<td>(0)</td>
<td>NR</td>
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<tr>
<td>Shelton 2001</td>
<td>8</td>
<td>197</td>
<td>OLZ 6-18mg/d</td>
<td>NR</td>
<td>(12.1)</td>
<td>NR</td>
<td>(11.1)</td>
<td>(39.7)</td>
<td>(13.1)</td>
<td>NR</td>
<td>NR</td>
<td>(0)</td>
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<tr>
<td>Ferren 2001</td>
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<td>FLX 20-60mg/d</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>8</td>
<td>OLZ 5-20mg/d</td>
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<td>FLX 20mg/d</td>
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<td>3 (7.8)</td>
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<td>8 (21)</td>
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<tr>
<td></td>
<td>6</td>
<td>34</td>
<td>MIN 60mg/d</td>
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</tr>
<tr>
<td>Trivedi 2006</td>
<td>12</td>
<td>238</td>
<td>SER 50-200mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11 (4.6)</td>
<td>2 (0.84)</td>
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<tr>
<td>Thase 2007</td>
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<td>BUP 150-400mg/d</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
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<td>2 (0.83)</td>
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<td>2 (0.83)</td>
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<td>12</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>6 (17)</td>
<td>0</td>
<td>NR</td>
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</table>

A/E = adverse event; BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; FLX = fluoxetine; GI = gastrointestinal; MIN = mianserin; mg/d = milligrams per day; n = sample size; NR = not reported; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PLZ = phenelzine; SER = sertraline; TCP = tranylcypromine; VEN = venlafaxine; VEN-ER = venlafaxine extended release

*Complete study sample size.

^At least one serious event and includes a combination of events requiring hospitalization for psychiatric event (including for suicidal ideation), death or medical event.
Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
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<tr>
<td><strong>Adding SSRI</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura82,83</td>
<td>5 days</td>
<td>18</td>
<td>SSRI + PBO (saline)</td>
<td>0</td>
<td>3 (18.2)</td>
<td>2 (11.1)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>7 (39)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>SSRI + CIT 10mg in 250ml of saline</td>
<td>2 (11.1)</td>
<td>0</td>
<td>0</td>
<td>3 (16.7)</td>
<td>NR</td>
<td>1 (5.6)</td>
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<td>9 (50)</td>
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<tr>
<td>Altamura82,83</td>
<td>5 days</td>
<td>18</td>
<td>SSRI + PBO (saline)</td>
<td>NR</td>
<td>3 (18.2)</td>
<td>2 (11.1)</td>
<td>NR</td>
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<td>NR</td>
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<td>7 (39)</td>
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<td>SSRI + CM 25mg in 250ml of saline (intravenous)</td>
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<td>5 (27.8)</td>
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<td>NR</td>
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<td>18 (54.5)</td>
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<td>34</td>
<td>FLX 20mg/d, DES 25-50mg/d</td>
<td>10 (39.4)</td>
<td>9 (26.5)</td>
<td>6 (47.1)</td>
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<td>FLX 20mg + DES 25-50mg/d</td>
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<tr>
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<td>11 (4.6)</td>
<td>2 (0.84)</td>
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<td></td>
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<td>250</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5 (2)</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>239</td>
<td>BUP 150-400mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 (2.5)</td>
<td>2 (0.83)</td>
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</tr>
<tr>
<td>Trivedi113</td>
<td>12</td>
<td>279</td>
<td>CIT + BUP, 200-400mg/d</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>10 (3.6)</td>
<td>11 (3.9)</td>
<td>1 (0.36)</td>
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</tbody>
</table>
Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
</tr>
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<tbody>
<tr>
<td>Preskorn$^{80}$ 2008</td>
<td>6</td>
<td>15</td>
<td>PAX 40mg + PBO</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>2 (13)</td>
<td>NR</td>
<td>NR</td>
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<tr>
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<td>15</td>
<td>PAX 40mg + CP-101606 infusion/ duration to 1.5h and the dose to 0.5mg/kg/h</td>
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<td>NR</td>
<td>NR</td>
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<td>6 (40)</td>
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<td>6 (60)</td>
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<td>NR</td>
<td>5 (45)</td>
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<td>Michelson$^{87,101,132}$ 2007</td>
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<td>74</td>
<td>SER 100mg/d + PBO</td>
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<td>12 (16)</td>
<td>1 (1.3)</td>
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<td>SER 100mg/d + AM 40mg/d</td>
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<td>NR</td>
<td>18 (25)</td>
<td>8 (11)</td>
<td>NR</td>
<td>4 (5.6)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Shapira$^{89}$ 2006</td>
<td>4</td>
<td>9</td>
<td>SSRI + PBO</td>
<td>1 (11.1)</td>
<td>NR</td>
<td>NR</td>
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<td>SSRI + PHN</td>
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<td>NR</td>
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<td>Seidman$^{91}$ 2005</td>
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<td>SSRI + PBO volume matched (injection)</td>
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<td>NR</td>
<td>NR</td>
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<td>Fava$^{114}$ 2005</td>
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<td>13 (9)</td>
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Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies (continued)

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<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n·</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
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<td>Nemets123 1999</td>
<td>4 18</td>
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<td>SSRI original dose + PBO</td>
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<td>1/19 (5.2)</td>
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<td>NR</td>
<td>NR</td>
<td>1 (5.5)</td>
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<td>18 IN 12gm/d, SSRI original dose</td>
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<td>2 (11.1)</td>
<td>NR</td>
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<tr>
<td>Dunner86 2007</td>
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<td>SER 100-200mg/d</td>
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<td>1 (5)</td>
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<td>8 (40)</td>
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<td>Adding Atypical Antipsychotics</td>
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<td>Thase88 2007</td>
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<td>FLX 50mg/d</td>
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<td>NR</td>
<td>(2.4)</td>
<td>(6.8)</td>
<td>(19.4)</td>
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<td>197 OLZ 6-18mg/d</td>
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<td>(12.1)</td>
<td>NR</td>
<td>(11.1)</td>
<td>(39.7)</td>
<td>(13.1)</td>
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<td>198 OLZ 6-18mg/d + FLX 50mg/d</td>
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<td>(10.5)</td>
<td>(35)</td>
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<tr>
<td>Shelton122 2001</td>
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<td>FLX 20-60mg/d</td>
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<td>10 OLZ 5-20mg/d, FLX 20-60mg/d</td>
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<td>Rush44 2006</td>
<td>12 238</td>
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<td>5 (2)</td>
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<td>239 BUP 150-400mg/d</td>
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<td>2 (0.83)</td>
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<td>Trivedi113 2006</td>
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<td>CIT + BUS, 200-400mg/d</td>
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<td>12 (4.2)</td>
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<td>Appelberg120 2001</td>
<td>6 51</td>
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<td>CIT 40mg/d/FLX 35.4mg/d + PBO</td>
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<td>NR</td>
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Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies (continued)

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<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
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<tbody>
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<td>Landén</td>
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<td>51</td>
<td>CIT 40mg/d/FLX 35.4mg/d + BUS 35-47mg/d</td>
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<td>Landén</td>
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<td>60</td>
<td>CIT 46.1mg/d or PAX 39.8mg/d + PBO</td>
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<td>30 (58)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>23 (44)</td>
<td>NR&lt;sup&gt;5&lt;/sup&gt;</td>
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<td>57</td>
<td>CIT 46.1mg/d or PAX 39.8mg/d + BUS 49mg/d</td>
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<td>NR</td>
<td>NR</td>
<td>23 (38)</td>
<td>NR&lt;sup&gt;#&lt;/sup&gt;</td>
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<td>Fava</td>
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<td>15</td>
<td>FLX 40-60mg/d</td>
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<tr>
<td>Fava</td>
<td>12</td>
<td>33</td>
<td>FLX 40-60mg/d + Li 300-600mg/d</td>
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<td>6 (18.2)</td>
<td>18 (54.5)</td>
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<tr>
<td>Fava</td>
<td>12</td>
<td>34</td>
<td>FLX 20mg/d, Li 300-600mg/d</td>
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<td>PAX 30mg/d + Li;</td>
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Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies (continued)

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<th>Study</th>
<th>Duration (Weeks)</th>
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<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
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<td>SSRI + PI Total = only SSRI doses given, PI dose not reported; Group 1 = FLX 20-60mg, PAX 20mg, SER 150-200mg;</td>
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<td>10 (10.2)</td>
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<td>7 (7.1)</td>
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<td>54 (55)</td>
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<td>SER 100mg/d + MIN</td>
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<td>45 (45.9)</td>
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<td>9 (9.2)</td>
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</table>
Table 29. Summary of reported rates of harms for studies comparing monotherapy to combined therapies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n*</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carta127 2008</td>
<td>32</td>
<td>10</td>
<td>SSRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>SSRI + Exercise</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lynch128 2007</td>
<td>54</td>
<td>12</td>
<td>SSRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>SSRI + DBT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Wiles94 2008</td>
<td>16</td>
<td>9</td>
<td>SSRI</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>SSRI + CBT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rush44 2006</td>
<td>12</td>
<td>238</td>
<td>SER 50-200mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>11 (4.6)</td>
<td>2 (0.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250</td>
<td>VEN 37.5-375mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5 (2)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>239</td>
<td>BUP 150-400mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 (2.5)</td>
<td>2 (0.83)</td>
</tr>
<tr>
<td>Thase110 2007</td>
<td>12</td>
<td>86</td>
<td>Medications Monotherapy</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>23^ (27, 652, 75306)</td>
<td>2^</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>CBT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 (17)</td>
<td>0^</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
<td>CIT + CBT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 (9)</td>
<td>4^</td>
</tr>
<tr>
<td></td>
<td></td>
<td>117</td>
<td>Combined medications</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>22 (19)</td>
<td>4^</td>
</tr>
</tbody>
</table>

A/E = adverse event; BUP = bupropion; BUS = buspirone; CM = clomipramine; CIT = citalopram; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; DES = desipramine; FLX = fluoxetine; GI = gastrointestinal; IN = inositol; LI = lithium; MIN = mianserin; MOD = modafinil; n = sample size; NR = not reported; OLZ = olanzapine; PAX = paroxetine; PBO = placebo; PHN = Phenytoin; PI = pindolol; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; TE = testosterone; VEN = venlafaxine; ZI = ziprasidone
*Exited because of intolerance.
At least one serious event and includes a combination of events requiring hospitalization for psychiatric event (including for suicidal ideation), death or medical event.
^Indicates the patients reporting remittance from sexual dysfunction at 4 weeks (n=47) but not proportion that had dysfunction with the use of buspirone.
$Reported only baseline prevalence of sexual dysfunction.
Table 30. Summary of reported rates of harms for studies comparing combined therapy to other combined therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adding Non-SSRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altamura</td>
<td>5 days</td>
<td>18</td>
<td>SSRI + CIT 10mg in 250ml of saline</td>
<td>2 (11.1)</td>
<td>0</td>
<td>3 (16.7)</td>
<td>NR</td>
<td>1 (5.6)</td>
<td>NR</td>
<td>9 (50)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>SSRI + CM 25mg in 250ml of saline (intravenous)</td>
<td>0</td>
<td>3 (18.2)</td>
<td>2 (11.1)</td>
<td>0</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>7 (39)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Trivedi</td>
<td>12</td>
<td>286</td>
<td>CIT + BUS 15-60mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>12 (4.2)</td>
<td>12 (4)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>279</td>
<td>CIT + BUP, 200-400mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10 (3.6)</td>
<td>11 (3.9)</td>
<td>1 (0.36)</td>
</tr>
<tr>
<td>Dinan</td>
<td>1</td>
<td>6</td>
<td>SER 100-200mg/d + LI 400mg/d</td>
<td>NR</td>
<td>NR</td>
<td>1 (16.1)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1 (16.1)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>SER 100-200mg/d + LI 800mg/d</td>
<td>NR</td>
<td>NR</td>
<td>3 (60)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3 (60)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Dunner</td>
<td>8</td>
<td>21</td>
<td>SER 100-200mg/d + ZI 40-80mg/d</td>
<td>5 (22.7)</td>
<td>5 (22.7)</td>
<td>4 (18.10)</td>
<td>8 (36.4)</td>
<td>NR</td>
<td>4 (18.2)</td>
<td>NR</td>
<td>21 (100)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19</td>
<td>SER 100-200mg/d + ZI 80-160mg/d</td>
<td>3 (26.3)</td>
<td>3 (15.8)</td>
<td>5 (26.4)</td>
<td>6 (31.6)</td>
<td>NR</td>
<td>3 (15.8)</td>
<td>NR</td>
<td>16 (84)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fava</td>
<td>12</td>
<td>33</td>
<td>FLX 20mg/d, DES 25-50mg/d</td>
<td>10 (39.4)</td>
<td>9 (26.5)</td>
<td>6 (47.1)</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>FLX 20mg/d, LI 300-600mg/d</td>
<td>0</td>
<td>11 (32.4)</td>
<td>17 (50)</td>
<td>NR</td>
<td>NR</td>
<td>9 (26.5)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fava</td>
<td>4</td>
<td>12</td>
<td>FLX 20mg + DES 25-50mg/d</td>
<td>1 (8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>FLX 20mg/d + LI 300-600mg/d</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</tr>
</tbody>
</table>
Table 3. Summary of reported rates of harms for studies comparing combined therapy to other combined therapies (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (Weeks)</th>
<th>n</th>
<th>Comparison and Dose (mg/d)</th>
<th>Anxiety n (%)</th>
<th>Sedation n (%)</th>
<th>GI Problems n (%)</th>
<th>Sleep Problems n (%)</th>
<th>Weight Gain n (%)</th>
<th>Headache n (%)</th>
<th>Sexual Dysfunction n (%)</th>
<th>Withdrawals Due To A/E n (%)</th>
<th>Serious Events n (%)</th>
<th>Suicide n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivedi\textsuperscript{113} 2006</td>
<td>12</td>
<td>286</td>
<td>CIT + BUS 15-60mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>12 (4.2)</td>
<td>12 (4)</td>
<td>4 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Thase\textsuperscript{110} 2007</td>
<td>239</td>
<td>CIT + BUP, 200-400mg/d</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10 (3.6)</td>
<td>11 (3.9)</td>
<td>1 (0.36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thase\textsuperscript{110} 2007</td>
<td>12</td>
<td>117</td>
<td>Medications Combined</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>22 (19)</td>
<td>4^</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>CIT + CBT</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>6 (9)</td>
<td>4^</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A/E = adverse event; BUP = bupropion; BUS = buspirone; CM = clomipramine; CIT = citalopram; CBT = cognitive behavioral therapy; DES = desipramine; FLX = fluoxetine; GI = gastrointestinal; LI = lithium; mg/d = milligrams per day; NR = not reported; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; ZI = ziprasidone

^At least one serious event and includes a combination of events requiring hospitalization for psychiatric event (including for suicidal ideation), death or medical event.
KQ3. How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, ages, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)? These subgroups will be considered with respect to the different interventions.

**Key Messages**

- Overall, there is small number of studies that have evaluated the impact of disease type, disease severity, previous comorbidities, age, gender, and race on treatment outcomes.
- There is some evidence from the STAR*D level 2 cohort that would suggest that persons with concurrent anxiety symptoms have less likelihood of achieving remission.
- There is some evidence from the TORDIA trial that milder depression, less family conflict, and absence of suicidal behavior are associated with greater likelihood of a positive treatment response at 12 weeks in adolescents.
- Given that there was one study each for adults with dysthymia and subsyndromal depression, this review is limited in its ability to meaningfully compare conclusions across populations with different depressive disorders. There are 7 studies (13 publications) that undertook stratified or subgroup analyses evaluating factors that may impact treatment outcomes in adults, and 1 (3 publications) for adolescents.

**Comparison Across Different Treatment Populations in Adults**

**Baseline Disease Severity**

Six studies evaluated the impact of disease severity on treatment outcomes in adults. One study undertook a subgroup analysis on subjects with baseline HAMD-17 score greater than 17, and found that the group with combined treatment (SSRI + modafinil) had a statistically significant greater reduction (p = 0.05) relative to the SSRI group alone. Another study found that subjects with an initially higher MADRS score tended to show greater reductions in MADRS overall (p = 0.04), or within the first 2 weeks of treatment (MADRS >30) in the combined therapy group (fluoxetine/citalopram + buspirone) relative to subjects in the SSRI group with higher initial scores. One study (3 publications) found that a lower baseline HAMD-17 score was predictive of response for the fluoxetine group (p = 0.008) and the lithium augmentation group (p = 0.04) but not the desipramine group; a reanalysis found that the odds ratio (OR) for augmentation strategy relative to a dose increase in fluoxetine (OR = 0.85, 95% CI 0.76 to 0.96). One of these studies found that the age of onset of depression was predictive of response (p = 0.009).

Analysis of level 2 STAR*D cohort found that subjects with severe depression (QID-SR 16 or greater) were less likely to achieve remission (OR = 0.34 [95% CI 0.22 to 0.52]); however, this aspect was not valuable in assisting clinicians in recommending any monotherapy treatment (sertraline, venlafaxine, or bupropion). Greater baseline symptom severity was also associated with greater rates of attrition.

Two studies evaluated baseline HAMD scores (>23) and baseline severity and showed that these did not affect treatment response.
Previous History of Failure

Two studies\textsuperscript{81,88} evaluated previous history of failure. One study undertook a subgroup analysis evaluating the drug class of previous failure (SSRI versus other); this study showed differences with the combined olanzapine-fluoxetine group achieving a statistically significant greater reduction on the MADRS relative to the fluoxetine or olanzapine monotherapy groups.\textsuperscript{88} This trend was observed in the nonSSRI group for those with at least one previous failure, but only for olanzapine and not fluoxetine.\textsuperscript{88}

In the STAR*D level 2 cohort, intolerance to citalopram (OR = 1.57 (95% CI 1.11 to 2.21)) or response to citalopram during level 1 (OR = 2.78 [95% CI 1.77 to 4.38]) increased the likelihood of remission; however, this was not practically helpful to clinicians in selecting one monotherapy treatment over the other.\textsuperscript{81}

Comorbidities

The STAR*D cohort analysis for level 2 subjects on monotherapies (sertraline, venlafaxine, and bupropion), showed that remission was less likely in patients with other concurrent psychiatric disorders (specifically panic or post-traumatic disorders, generalized anxiety disorders, obsessive compulsive disorders, social phobia, or anxious or melancholic features).\textsuperscript{81} The overall OR for presence of anxious, atypical, or melancholic features were 0.30 (95% CI 0.20 to 0.45), 1.04 (95% CI 0.67 to 1.61), and 0.43 (95% CI 0.25 to 0.73), respectively.\textsuperscript{81}

A more detailed analysis of the STAR*D level 2 cohort showed that the rates of remission were significantly less for anxious patients relative to nonanxious patients across all five pharmacological treatment arms (both monotherapy and combined therapy).\textsuperscript{99} Logistic regressions, however, indicated only a moderate effect of anxiety, suggesting that there was no advantage of one treatment over another in subjects with anxious depression.\textsuperscript{99}

One study showed no significant difference on treatment response for subjects with melancholic features.\textsuperscript{119}

Age

Two studies showed no statistical difference when the impact of age on treatment response was evaluated.\textsuperscript{116,118,119} Analysis of the STAR*D level 2 cohort showed that an age younger than 35 increased the likelihood of remission (OR varying from 1.43 [95% CI 0.78 to 3.59] to 1.81 [95% CI 0.97 to 3.38]).\textsuperscript{81} In contrast, younger age was associated with attrition for the augmentation treatment group.\textsuperscript{102}

Gender

Three studies evaluated gender\textsuperscript{92,97,116,118,119,130} and showed no statistical difference on treatment response. The STAR*D cohort at level 2 estimated an OR of 0.96 (95% CI 0.69 to 1.35); overall, gender was not an important factor in helping to select the optimal monotherapy.\textsuperscript{81}

Race

Nonwhite races were associated with greater rates of attrition for level 2 STAR*D subjects;\textsuperscript{102} conversely, white race was associated with greater likelihood of remission.\textsuperscript{81}

Comparison Across Different Populations in Adolescents

Neither of the two studies evaluating children and adolescents assessed specific subgroups with respect to baseline severity, previous failures, age, and race as predictors of response. The
TORDIA trial\textsuperscript{42,138,140,141,144-149} provided some evidence for other predictors of treatment response and showed that milder depression, less family conflict, and absence of suicidal behavior were associated with greater likelihood of a positive treatment response at 12 weeks. Conversely, a subgroup with substance abuse impairment was shown to be associated with greater depression severity at baseline, older age, family conflict, physical/sexual abuse, and comorbid oppositional defiant disorder.\textsuperscript{145} No relationship was observed between FKBP5 polymorphisms and suicidal events.\textsuperscript{144}

In the context of combined treatment of CBT with antidepressants, adolescents with no history of abuse and few comorbidities had a greater probability of a positive response.\textsuperscript{141} Compared with adolescents with a history of physical or sexual abuse, those without had a threelfold rate (OR = 2.8 95\% CI 1.6 to 4.7) of positive response to combination therapy versus monotherapy.\textsuperscript{148} Those with a history of sexual abuse had similar response rates to either combination (with CBT) or medication therapy.\textsuperscript{148} In contrast, those with physical abuse had a lower rate of response to combination therapy relative to antidepressants alone; even after adjustment for other clinical predictors, adolescents with a history of physical abuse seemed to predict a poorer outcome for combination therapy.\textsuperscript{148} Older youths (age 18 to 19) (OR 3.7 [95\% CI 1.2 to 12.0]) with more comorbidities are more likely to benefit from combined treatment.\textsuperscript{141}

In the TORDIA trial, adolescents who had not responded by 6 weeks had their antidepressant dose increased. A dose increase at 6 weeks for those on citalopram or fluoxetine were most likely to result in a response when it led to a change in plasma concentration greater than or equal to the geometric mean.\textsuperscript{147} This was not the case for paroxetine or venlafaxine.\textsuperscript{147}

**KQ4. What is the range of recommended clinical actions following the failure of one adequate course of SSRI based on current clinical practice guidelines published between 2004 and A?**

**Key Messages**

There were 27 clinical practice guidelines (CPGs) (18 for adults, seven for adolescents, and two including both) providing recommendations for patients with MDD. Four CPGs for adults and three for adolescents did not provide any recommendations for patients with previous inadequate responses. Four guidelines included patients with dysthymia and subsyndromal depression but no recommendations for these subgroups who had failed previous treatment for both adults and adolescents. The majority of the CPGs did not specify a definition for inadequate response.

All CPGs for adults and adolescents were applicable to patients from primary care and outpatient settings; a smaller number indicated applicability to inpatient settings. For adults, the majority of CPGs did not specify any type of antidepressant when recommending switching to monotherapy strategies. Increasing the dose and duration was frequently recommended but the interval or change in dose was not specified in the majority of guidelines.

When combined therapy was recommended there was a greater tendency to specify the drug for adding to antidepressants. However, there was great variability in the augmenting agents recommended.

For adolescents, there was an approximately equal number of CPGs that specified which agents to consider for monotherapy and which to consider for combined therapies. There was a preference to commence treatment using nonpharmacological interventions. Some guidelines cited adult evidence as the evidentiary basis for suggesting treatment strategies.
Recognizing that clinicians have a number of treatment options to addressing patients with an inadequate response, we thought it would be important to evaluate current recommendations within CPGs regarding the optimal approach to treatment in patients with inadequate response. Our goal was to identify and critically appraise the “rigor” of these recommendations, and contrast and compare them for this failed response subgroup.

There were a total of 27 CPGs (33 publications) eligible for review. There were seven CPGs that were specific only to adolescents, 13,14,172-176 18 CPG (24 publications) for adults alone,53-55,151-171 and two applicable to both adults and adolescents.177,189

Note that CPGs can be published as a comprehensive single document with numerous recommendations for different interventions, or as multiple documents related to different interventions but sponsored by the same organization and published in the same year. For the purposes of this review, we grouped publications based on unique content; any documents that summarized guidelines or specified recommendations for subgroups of patients included in the primary document were considered as companion publications to the main CPGs. There are six guidelines published by the National Institute of Clinical Excellence (NICE) for adults that are interrelated, and from these we evaluated only two publications as representative CPGs (guidelines 90164 and 97162). NICE guideline 90 is an update of the evidence and recommendations for subjects with MDD;164 summaries and quick references of these recommendations are published in guideline 23.168,169 NICE guideline 91171 is a summary of recommendations for depression in adults with chronic physical health problems and refers to recommendations in guidelines 90164 and 97.162 NICE guideline 97162 specifies recommendations for CBT. One companion paper summarizes recommendations for guidelines 90 and 91.170 Similarly, the American Psychological Association (APA) has updated their guidelines166 and the previous guideline167 was considered a companion.

There were six publications53,54,159,190-192 related to the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines, three were recommendations53,54,159 and three publications54,191,192 provide supporting documentation for the methods used in the guidelines. One publication is a summary companion paper158 of another CPG from the American College of Physicians (ACP).55 In the guidelines for adolescents, two publications172,174 are from the Guidelines for Adolescent Depression in Primary Care (GLAD-PC) and two are from the United States Preventative Services Task Force (USPSTF).13,14

Figure 2 shows that 59 guidelines were excluded because of the following: 1) publication prior to 2004 (n=45); 2) exclusive focus on diagnosis or screening rather than treatment (n=7); 3) not a population of interest (n=4); and, 4) an algorithm (n=3).

**CPGs Specific for MDD, Dysthymia, and Subsyndromal Depression in Adults**

**Characteristics of CPGs for Adults**

Table 31 shows the characteristics of the CPGs as a function of country of origin, setting, and intended users. All 18 CPGs were applicable to adults with MDD. Four CPGs make note of dysthymia or subthreshold depression,55,164,177,189 but not all provide recommendations for those that had failed response to previous treatments. Similarly, an earlier version of the APA guideline167 discusses these subtypes but the most recent update focuses only on MDD.166
Dysthymia and Subsyndromal Depression

One CPG provided a general definition of dysthymia (not distinguishing this from minor depression) and recommended second- and third-line interventions following lack of sufficient response to a pharmacological agent or a psychological intervention. One CPG considered subthreshold persistent symptoms as a distinct subgroup of patients and noted the lack of clarity in studies that included subjects traditionally diagnosed with dysthymia (although the studies they evaluated used this classification, some studies do not distinguish this from minor depression). The lack of consistency in defining dysthymia and subthreshold depressive symptoms is noted, as is the potential lack of natural discontinuity between subthreshold depressive symptoms and MDD in the context of routine clinical practice. This CPG provided recommendations for those patients who had failed to respond to low-intensity psychosocial interventions or other interventions; it is not clear if other interventions includes failure to an SSRI. This CPG does not recommend the use of pharmacological treatment for subthreshold symptoms and as such would not make recommendations for dysthymia patients who have failed pharmacological treatment.

Three guidelines discuss dysthymia but do not provide any recommendations for treatment in those who fail to respond: one CPG specifies dysthymia as distinct from MDD (and can be present concurrently (double depression)); however, in the update of this guideline there was no further discussion of dysthymia. Another CPG indicates that dysthymia is distinct from MDD, and is characterized by persistent symptoms for greater than 2 years and further includes this diagnostic category under the label of subthreshold depression (includes minor depression and other nonspecified categories). One CPG summarizes evidence on pharmacological treatment that includes both MDD and dysthymia but presents no recommendations specific to dysthymia.

MDD Populations

All of the CPGs for adults with MDD were applicable to patients from primary care and outpatient settings; six guidelines indicating applicability to inpatient settings (Table 31). All of the CPGs were intended primarily for, or were applicable to, primary care practitioners, with the exception of one CPG that was developed specifically for psychiatrists. The majority of guidelines were undertaken in the United States (n=6), one was developed by the Singapore Ministry of Health, one was an international consensus statement at a meeting sponsored by a drug manufacturer, one developed in Germany, and one by the World Federation of Biological Psychiatry.

All but two of the 18 guidelines considered a variety of treatment interventions for adult MDD; these two CPGs evaluated solely pharmacological interventions, and computerized CBT. The other CPGs gave treatment recommendations that included a variety of pharmacological, psychological, and CAM interventions. However, the majority of recommendations were not applicable to patients who had had inadequate responses to previous pharmacological treatment. When recommendations were specific to patients who had previous inadequate response, none were distinguished by different classes of antidepressants.
Table 31. Characteristics of included CPGs showing country, disorder type included, setting, and intended guideline users

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Adult United States</th>
<th>Adult Canada</th>
<th>Adult United Kingdom</th>
<th>Adult New Zealand/ Australia</th>
<th>Adult Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>Jaehne(^{55})</td>
<td>Ravindran(^{54})</td>
<td>Anderson(^{177})</td>
<td>Ellis(^{156})</td>
<td>Bauer(^{154})</td>
</tr>
<tr>
<td></td>
<td>Qaseem(^{55})</td>
<td>Parikh(^{54})</td>
<td>NICE(^{164,168-171})</td>
<td>Malhi(^{157})</td>
<td>Mahendran(^{161})</td>
</tr>
<tr>
<td></td>
<td>Steinman(^{155})</td>
<td>Lam(^{159})</td>
<td>NICE(^{162})</td>
<td>NZGG(^{189})</td>
<td>Nutt(^{163})</td>
</tr>
<tr>
<td></td>
<td>Gelsenburg(^{166})</td>
<td>Conn(^{160})</td>
<td></td>
<td></td>
<td>Harter(^{165})</td>
</tr>
<tr>
<td>Dysthymia/Subthreshold depression*</td>
<td>Karasu(^{167})</td>
<td>Anderson(^{177})</td>
<td>NICE(^{164,168-171})</td>
<td>NZGG(^{189})</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Qaseem(^{55})*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Setting                           | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|-----------------------------------| Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{164,168-171}\) | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Horsley\(^{193}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | USPSTF\(^{168}\)    | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
|                                   | Steinman\(^{155}\)  |                  |                      |                             |             |
|                                   | Davidson\(^{155}\)  |                  |                      |                             |             |
|                                   | Gelsenburg\(^{166}\) |                  |                      |                             |             |
| Primary Care                      | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|                                   | Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{164,168-171}\) | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Horsley\(^{193}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | USPSTF\(^{168}\)    | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
|                                   | Steinman\(^{155}\)  |                  |                      |                             |             |
|                                   | Davidson\(^{155}\)  |                  |                      |                             |             |
|                                   | Gelsenburg\(^{166}\) |                  |                      |                             |             |
| Outpatient MH                     | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|                                   | Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{164,168-171}\) | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Anderson\(^{177}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | Gelsenburg\(^{166}\) | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
| Inpatient MH                      | Qaseem\(^{55}\)     | Parikh\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             |             |
|                                   | Gelsenburg\(^{166}\) | Conn\(^{160}\) |                      |                             |             |
| Other                             |                     |                |                      |                             |              |

| Intended Users                    | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|-----------------------------------| Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{169}\)      | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Horsley\(^{193}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | USPSTF\(^{168}\)    | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
|                                   | Steinman\(^{155}\)  |                  |                      |                             |             |
|                                   | Davidson\(^{155}\)  |                  |                      |                             |             |
|                                   | Gelsenburg\(^{166}\) |                  |                      |                             |             |
| Primary Care Physicians           | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|                                   | Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{169}\)      | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Horsley\(^{193}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | USPSTF\(^{168}\)    | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
|                                   | Steinman\(^{155}\)  |                  |                      |                             |             |
|                                   | Davidson\(^{155}\)  |                  |                      |                             |             |
|                                   | Gelsenburg\(^{166}\) |                  |                      |                             |             |
| Mental Health Specialists         | Jaehne\(^{151}\)     | Ravindran\(^{54}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |
|                                   | Qaseem\(^{55}\)     | Parikh\(^{54}\) | NICE\(^{169}\)      | Malhi\(^{157}\)             | Mahendran\(^{161}\) |
|                                   | Horsley\(^{193}\)  | Lam\(^{159}\) | NICE\(^{162}\)      |                             | Nutt\(^{163}\) |
|                                   | USPSTF\(^{168}\)    | Conn\(^{160}\) |                      |                             | Harter\(^{165}\) |
|                                   | Steinman\(^{155}\)  |                  |                      |                             |             |
|                                   | Davidson\(^{155}\)  |                  |                      |                             |             |
|                                   | Gelsenburg\(^{166}\) |                  |                      |                             |             |
| Allied Mental Health disciplines  | Jaehne\(^{151}\)     | Parikh\(^{53}\) | Anderson\(^{177}\)  | Ellis\(^{156}\)             | Bauer\(^{154}\) |

NICE = National Institute for Clinical Excellence; NZGG = New Zealand Guidelines Group; USPSTF = United States Preventive Task Force Services

*Dysthymia population included in the CPG but no recommendations are specific to dysthymia patients who failed to respond to treatment on an SSRI.

Inadequate Response

From 18 CPGs, eight defined response as a 50 percent or greater reduction in symptoms (as measured on a standardized rating scale), and partial response as a 25 to 50 percent reduction in symptoms.\(^{53,54,151,154,159,166,177,189}\) One CPG specified that the measure should be a change in the
Patient Health Questionnaire – 9. The CANMAT CPG recommendations were intermingled with order of treatment and lack of adequate response. First line treatment is identified as those interventions for which there is the best evidence of efficacy balanced with good safety and tolerability. Second- and third-line treatments are defined as those reserved for situations where first-line treatments are not indicated, cannot be used, or when first-line treatments are not effective. As such, for the CANMAT guidelines specific to CAM and psychological therapies the ‘failed to respond populations’ are not identified clearly within the body of the recommendations; we must assume that second- and third-line therapies are applicable to those that failed previous pharmacological treatments. One CPG notes the inconsistency in defining lack of response, but opts to categorize patients in the context of next step treatment options. Four CPGs did not include recommendations specific to failed response populations, and as such, a definition may not have been necessary. The remaining nine CPGs did not report a specific definition, and as such inadequate response and suggest variable operationalization of this for clinicians. One CPG emphasizes that response should be assessed with the use of a structured measure, but provides no recommendation as to the measure or threshold for definition.

For those CPGs that did report a formal definition of inadequate response, only two provided clear indications for differential treatment strategies for those with partial versus nonresponse. Eight CPG indicated that the definition of inadequate response was linked to failure following time intervals varying from 2 to 4 weeks, 4 to 6 weeks of significant improvement, 4 to 8 weeks, and 6 to 8 weeks of partial improvement.

Quality Assessment of CPGs for Adults

Table 32 shows the domain scores for the AGREE II ratings of the CPGs for adults. The AGREE II is based on six domains of methodology for the guideline process and one item with an overall assessment. All CPGs scored high for *scope and purpose* (Domain 1) (range 69 to 100 percent).

*Stakeholder involvement* (Domain 2) showed scores varying from 39 to 92 percent, and the lowest score was for a CPG sponsored by CANMAT making recommendations for the use of complementary and alternative treatments for MDD. Only six from 18 CPG indicated that patient’s views and preferences had been sought (score five or greater). For the domain of *rigor of development* (Domain 3), scores varied from zero to 85 percent; all but three CPG did not indicate a process for updating the guideline. For the domain of *clarity of presentation* (Domain 4), scores were generally high and varied from 61 to 94 percent. This domain evaluated whether the recommendations were clear and unambiguous, such that options were clearly presented, and key recommendations easily identifiable. However, the scores for the items within this domain were based on all recommendations within the CPG and were not specific to those applicable to patients who failed to respond to antidepressants.

When considering the *applicability* domain (Domain 5), scores were highly variable from zero to 89 percent. The majority of CPGs scored poorly for two criteria within this domain: 1) consideration of potential resource implications of applying their recommendations, and 2) presenting monitoring or auditing criteria. For the domain regarding *editorial independence* (Domain 6), scores were highly variable and ranged from four to 96 percent. In particular, potential competing interests of the guideline development group were not consistently recorded.

Note that although the AGREE II evaluates the methodology of the guideline process, it cannot evaluate the clinical merit (taking into account the methods for summarizing the evidence)
and overall quality of the recommendations themselves. All of the CPGs had methods to establish the strength of the evidence, but they could not be compared with each other. Most systems of grading the strength of the evidence included aspects of study design, number of studies, or confidence of treatment; most included a level that reflected consensus or expert opinion for some recommendations.

Table 32. Scores from the AGREE II for CPG for adults

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Organization</th>
<th>Scope and Purpose (Domain 1)</th>
<th>Stakeholder Involvement (Domain 2)</th>
<th>Rigor of Development (Domain 3)</th>
<th>Clarity of Presentation (Domain 4)</th>
<th>Applicability (Domain 5)</th>
<th>Editorial Independence (Domain 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaehne 2009</td>
<td>Institute for Clinical Systems Improvement</td>
<td>97.22</td>
<td>88.89</td>
<td>82.29</td>
<td>75.00</td>
<td>68.18</td>
<td>95.83</td>
</tr>
<tr>
<td>Qaseem 2008</td>
<td>American College of Physicians</td>
<td>94.44</td>
<td>58.33</td>
<td>59.38</td>
<td>77.78</td>
<td>11.36</td>
<td>87.50</td>
</tr>
<tr>
<td>National Guideline Clearing House 2004</td>
<td>Kaiser Permanente</td>
<td>97.22</td>
<td>63.89</td>
<td>80.21</td>
<td>94.44</td>
<td>2.08</td>
<td>79.17</td>
</tr>
<tr>
<td>Steinman 2007</td>
<td>Centre for Disease Control</td>
<td>97.22</td>
<td>63.89</td>
<td>66.67</td>
<td>94.44</td>
<td>65.91</td>
<td>50.00</td>
</tr>
<tr>
<td>Davidson 2006</td>
<td>National Heart, Lung, and Blood Institute</td>
<td>91.67</td>
<td>61.11</td>
<td>42.71</td>
<td>80.56</td>
<td>0.00</td>
<td>12.50</td>
</tr>
<tr>
<td>Ravindran 2009</td>
<td>Canadian Network for Mood and Anxiety Treatments</td>
<td>86.11</td>
<td>38.89</td>
<td>68.75</td>
<td>80.56</td>
<td>2.27</td>
<td>70.83</td>
</tr>
<tr>
<td>Parikh 2009</td>
<td>Canadian Network for Mood and Anxiety Treatments</td>
<td>94.44</td>
<td>58.33</td>
<td>69.79</td>
<td>61.11</td>
<td>9.09</td>
<td>50.00</td>
</tr>
<tr>
<td>Lam 2009</td>
<td>Canadian Network for Mood and Anxiety Treatments</td>
<td>97.22</td>
<td>63.89</td>
<td>85.42</td>
<td>77.78</td>
<td>0.00</td>
<td>70.83</td>
</tr>
<tr>
<td>Conn 2006</td>
<td>Canadian Coalition for Seniors™ Mental Health</td>
<td>100.00</td>
<td>58.33</td>
<td>82.29</td>
<td>83.33</td>
<td>9.09</td>
<td>37.50</td>
</tr>
<tr>
<td>Anderson 2008</td>
<td>British Association for Psychopharmacology</td>
<td>91.67</td>
<td>58.33</td>
<td>72.92</td>
<td>91.67</td>
<td>2.27</td>
<td>12.50</td>
</tr>
<tr>
<td>NICE CBT 2009</td>
<td>National Institute for Clinical Excellence</td>
<td>97.22</td>
<td>88.89</td>
<td>77.08</td>
<td>88.89</td>
<td>70.45</td>
<td>50.00</td>
</tr>
<tr>
<td>NICE 2006</td>
<td>National Institute for Clinical Excellence</td>
<td>94.44</td>
<td>83.33</td>
<td>78.13</td>
<td>69.44</td>
<td>88.64</td>
<td>45.83</td>
</tr>
<tr>
<td>Ellis 2004</td>
<td>RANZCP</td>
<td>100.00</td>
<td>91.67</td>
<td>82.29</td>
<td>91.67</td>
<td>25.00</td>
<td>66.67</td>
</tr>
<tr>
<td>Malhi 2009</td>
<td>NSCCMHDA</td>
<td>100.00</td>
<td>66.67</td>
<td>69.79</td>
<td>91.67</td>
<td>11.36</td>
<td>66.67</td>
</tr>
<tr>
<td>New Zealand Guidelines Group 2008</td>
<td>Ministry of Health &amp; New Zealand Guidelines Group</td>
<td>100.00</td>
<td>66.67</td>
<td>69.79</td>
<td>88.89</td>
<td>43.18</td>
<td>100.00</td>
</tr>
<tr>
<td>Bauer 2007</td>
<td>World Federation of Societies of Biological Psychiatry</td>
<td>91.67</td>
<td>83.33</td>
<td>81.25</td>
<td>88.89</td>
<td>20.45</td>
<td>12.50</td>
</tr>
<tr>
<td>Mahendran 2005</td>
<td>Ministry of Health Singapore</td>
<td>94.44</td>
<td>41.67</td>
<td>0.00</td>
<td>66.67</td>
<td>0.00</td>
<td>4.17</td>
</tr>
<tr>
<td>Nutt 2010</td>
<td>International Consensus Group on Depression</td>
<td>94.44</td>
<td>69.44</td>
<td>12.5</td>
<td>77.78</td>
<td>54.45</td>
<td>66.67</td>
</tr>
<tr>
<td>Gelenburg 2010</td>
<td>American Psychiatric Association</td>
<td>97.22</td>
<td>55.56</td>
<td>84.38</td>
<td>80.56</td>
<td>27.27</td>
<td>91.67</td>
</tr>
<tr>
<td>Harter 2010</td>
<td>Association of Scientific Medical Societies of Germany and the German Association for Psychiatrists and Psychotherapy</td>
<td>69.44</td>
<td>61.11</td>
<td>48.96</td>
<td>80.56</td>
<td>27.27</td>
<td>91.67</td>
</tr>
</tbody>
</table>

NSCCMHDA = Northern Sydney Central Coast Mental Health Drug & Alcohol; RANZCP = Royal Australian and New Zealand College of Psychiatrists
**Recommendations of CPGs for Adults**

Four CPGs specific to MDD\(^{153,155,160,162}\) did not provide any recommendations for adult patients who had failed to respond to treatment. Two of these CPGs were specific to elderly patients in the community,\(^{153}\) and in long term care homes.\(^{160}\) One CPG had recommendations for patients with depression and cardiovascular disease,\(^{155}\) but none for those who had inadequate response to treatment. One CPG provided recommendations on the use of computerized CBT and was recommended for clients, which included only subjects with MDD or subthreshold symptoms that were not applicable to those who had failed previous treatment.\(^{162}\)

Table 33 shows the recommended strategies for both monotherapy and combined therapies. Attempts were made to identify any recommendations with regard to specific medications that were highlighted; however, for some guidelines it was not clear if the text following the recommendation (e.g., “switch antidepressants”) was a selective summary of the available evidence or an actual recommendation for action. The CANMAT CPGs recommended a stepped approach to treatment, intending a particular sequence of interventions (for example, second- and third-line therapies); however, there were several options within each of these categories.\(^{53,54,159}\) Two other guidelines specified a stepped approach\(^{164}\) or second- and third- line agents,\(^{189}\) but were less explicit as to which agents to consider. Other CPGs did not explicitly indicate an order of treatment other than cautioning to optimize initial treatment. Similarly, two CPGs did not explicitly recommend a change in dose or duration.\(^{55,154}\) Two other CPG distinguished between partial versus nonresponse and specified different treatment approaches to these.\(^{159,166}\)
Table 33. Recommendations for treatment in CPG that identified strategies for those that failed response

<table>
<thead>
<tr>
<th>Study</th>
<th>Starting Interval&lt;sup&gt;a&lt;/sup&gt; (Weeks)</th>
<th>Dose or Duration Change</th>
<th>Switch Other SSRI</th>
<th>Switch Non-SSRI</th>
<th>Switch to Augmenting Agent</th>
<th>Switch Nonpharm &amp; CAM</th>
<th>Add Augmentor</th>
<th>Add Other SSRI</th>
<th>Add Non-SSRI AD</th>
<th>Add Nonpharm &amp; CAM</th>
<th>Add Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaehne&lt;sup&gt;151&lt;/sup&gt; 2009</td>
<td>6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>PSY&lt;sup&gt;∗&lt;/sup&gt; LT&lt;sup&gt;∗&lt;/sup&gt; AC&lt;sup&gt;∗&lt;/sup&gt; ECT&lt;sup&gt;∗&lt;/sup&gt; VNS&lt;sup&gt;∗&lt;/sup&gt; DBS&lt;sup&gt;∗&lt;/sup&gt; rTMS MST</td>
<td>NS&lt;sup&gt;∗&lt;/sup&gt; TCA + T3&lt;sup&gt;∗&lt;/sup&gt; TCA + Li&lt;sup&gt;∗&lt;/sup&gt; AD + ARI&lt;sup&gt;∗&lt;/sup&gt; AD + AAP&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>SSRI + BUP&lt;sup&gt;∗&lt;/sup&gt; SSRI + MIR&lt;sup&gt;∗&lt;/sup&gt; SSRI + TCA&lt;sup&gt;∗&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaiser Permanente&lt;sup&gt;15&lt;/sup&gt; 2004</td>
<td>NS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>PSY</td>
<td>SSRI + Li (300 to 600mg/d)</td>
<td>SSRI + DES</td>
<td>PSY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qaseem&lt;sup&gt;55&lt;/sup&gt; 2008</td>
<td>6 to 8</td>
<td>CIT, FLX, FU, PAX, SER, MIR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>AD (non-MAO) + BUP SSRI + TCA or MIR MIR + VEN</td>
<td>PSY+ VNS ECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gelenburg&lt;sup&gt;166&lt;/sup&gt; 2010 Karasu&lt;sup&gt;167&lt;/sup&gt; 2009</td>
<td>4 to 8</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>QTP</td>
<td>AD + Li or T3, or BUS or AAP (OLZ, ARI, RIS, QTP) or MOD or STIM</td>
<td>X</td>
<td>AD + Li or T3, or AAP or BE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand/ Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellis&lt;sup&gt;156&lt;/sup&gt; 2004</td>
<td>NS</td>
<td>X</td>
<td>AD</td>
<td>AD</td>
<td>CBT</td>
<td>TCA + Li SSRI + Li or T3 or PI</td>
<td>SSRI + TCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malhi&lt;sup&gt;157&lt;/sup&gt; 2009</td>
<td>2 to 6</td>
<td>X</td>
<td>AD</td>
<td>AD</td>
<td>ECT</td>
<td>AD + Li or T3, or AAP or BE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand Guidelines Group&lt;sup&gt;189&lt;/sup&gt; 2008</td>
<td>3 to 6</td>
<td>X</td>
<td>AD/ VEN&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>AD/ TCA&lt;sup&gt;∗&lt;/sup&gt;</td>
<td>AD + Li</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Study started treatment from the moment of diagnosis or from the first stable treatment course.

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### Table 33. Recommendations for treatment in CPG that identified strategies for those that failed response (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Starting Interval* (Weeks)</th>
<th>Dose or Duration Change</th>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Switch Other SSRI</td>
<td>Switch NonSSRI</td>
<td>Switch to Augmenting Agent</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lam159 2009</td>
<td>1 to 4</td>
<td>X</td>
<td>ES SER VEN</td>
<td>DLX MIR MIL AMI or CM or MAO</td>
</tr>
<tr>
<td>Parikh53 2009</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ravindran54 2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson177 2008</td>
<td>4 to 8</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence164 2010</td>
<td>6 to 8</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
### Table 33. Recommendations for treatment in CPG that identified strategies for those that failed response (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Starting Intervala (Weeks)</th>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose or Duration Change</td>
<td></td>
<td>Add Other SSRI</td>
</tr>
<tr>
<td>Bauer164 2007</td>
<td>2 to 4</td>
<td>AD</td>
<td>AD + Li or T3, or AAP</td>
</tr>
<tr>
<td>Mahendran161 2005</td>
<td>4 to 8</td>
<td>X</td>
<td>AD + Li or T3</td>
</tr>
<tr>
<td>Nutt163 2010</td>
<td>4</td>
<td>X</td>
<td>AD + Li or AAP or T3</td>
</tr>
<tr>
<td>Harber165 2010</td>
<td>3 to 4 6 for elderly</td>
<td>X or TRP or VEN</td>
<td>AD + Li or MIN SSRI + MIR TCA + MIR</td>
</tr>
</tbody>
</table>

**Add Augmentor**

- **Other**
- **Add Other SSRI AD**
- **Add Nonpharm & CAM**
- **Add Other**

**Notes:**
- **AAP** = atypical antipsychotics; **ABNS** = ablative neurosurgery; **AD** = antidepressant; **AC** = acupuncture; **AG** = antiglucocorticoids; **AMI** = amitryptiline; **ARI** = aripiprazole; **BAC** = behavioral activation therapy; **BE** = benzodiazepine; **BIB** = bibliotherapy; **BUS** = buspirone; **BUP** = bupropion; **CBASP** = cognitive-behavioral analysis system of psychotherapy; **CBT** = cognitive behavioral therapy; **CIT** = citalopram; **CM** = clomipramine; **DBS** = deep brain stimulation; **DES** = desipramine; **DHEA** = dehydroepiandrosterone; **DLX** = duloxetine; **ECT** = electroconvulsive therapy; **ES** = estrogen; **EX** = exercise; **FA** = folic acid; **FLX** = fluoxetine; **FU** = fluvoxamine; **IPT** = Interpersonal therapy; **Li** = lithium; **LT** = light therapy; **LTG** = lamotrigine; **MAO** = monoamine oxidase inhibitor; **MBCT** = mindfulness-based cognitive therapy; **MIN** = mianserin; **MIL** = milnacipram; **MIR** = mirtazapine; **MOD** = modafinil; **MST** = magnetic seizure therapy; **NS** = Not significant; **OLZ** = olanzapine; **OM3** = omega-3; **PAX** = paroxetine; **PSY** = Psychotherapy; **QTP** = quetiapine; **RIS** = risperidone; **rTMS** = repetitive transcranial magnetic stimulation; **SAM-e** = S-adenosyl-L-methionine; **SER** = sertraline; **SleepD** = sleep deprivation; **SSRI** = selective serotonin reuptake inhibitors; **STIM** = Stimulants; **T3** = Tri-iodothyronine; **TCA** = tricyclic antidepressants; **TRP** = tryptophan; **VEN** = venlafaxine; **VNS** = vagal nerve stimulation; **ZI** = ziprasidone.

aThe time interval indicates the number of weeks following the first-line therapy attempt to initiate new treatment strategy.

**X** – Specified as a possible treatment approach for those with inadequate response.

*Applicable to Partial responders or treatment resistance and may require consultation with a specialist.

^Only for those that have failed two previous courses of antidepressants.

+Depression focused psychotherapy.
CPGs Specific to MDD and Dysthymia in Adolescents

Characteristics of CPG for Adolescents

There were seven CPGs that were specific only to adolescents,13,14,172-176 and two applicable to both adults and adolescents.177,189 Table 34 shows the characteristics of the adolescent CPGs, as a function of country of origin, setting, and intended users.

All seven CPGs applicable to adolescents included those with MDD. Two CPG had some recommendations applicable to patients with dysthymia13,177 and one also specified treatment for subsyndromal depression13 in adolescents. However, none of the recommendations were specific to those who had failed previous treatment.

All CPGs for adolescents were applicable to patients from primary care and outpatient settings, two guidelines indicating applicability to inpatient settings13,177 (Table 34). All CPG were intended primarily for or applicable to primary care practitioners, and three to specialists13,175,177 and allied mental health workers.13

The majority of guidelines were undertaken in the United States (n=6),13,14,172-175 two in the United Kingdom,176,177 and one in Australia and New Zealand.189

Table 34. Characteristics of CPG based on the type of disorder, the setting, and intended users

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Adolescent United States</th>
<th>Adolescent United Kingdom</th>
<th>Adolescent New Zealand/Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>Zuckerbrot172, Cheung174, U.S. Preventive Services14, Birmaher13, Hughes173, Gallagher176</td>
<td>Anderson177, National Institute for Clinical Excellence176</td>
<td>New Zealand Guidelines Group189</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>Birmaher13</td>
<td>Anderson177</td>
<td></td>
</tr>
<tr>
<td>Subsyndromal</td>
<td>Gallagher176</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Adolescent United States</th>
<th>Adolescent United Kingdom</th>
<th>Adolescent New Zealand/Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Care</td>
<td>Zuckerbrot172, Cheung174, U.S. Preventive Services14, Birmaher13, Hughes173, Gallagher176</td>
<td>Anderson177, National Institute for Clinical Excellence176</td>
<td>New Zealand Guidelines Group189</td>
</tr>
<tr>
<td>Outpatient MH</td>
<td>Birmaher13, Gallagher176</td>
<td>Anderson177</td>
<td></td>
</tr>
<tr>
<td>Inpatient MH</td>
<td>Birmaher13</td>
<td>Anderson177</td>
<td></td>
</tr>
</tbody>
</table>
Table 34. Characteristics of CPG based on the type of disorder, the setting, and intended users (continued)

<table>
<thead>
<tr>
<th>Intended Users</th>
<th>Adolescent United States</th>
<th>Adolescent United Kingdom</th>
<th>Adolescent New Zealand/Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Care Physicians</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuckerbrot172</td>
<td></td>
<td>Anderson177</td>
<td></td>
</tr>
<tr>
<td>Cheung174</td>
<td>U.S. Preventive Services14</td>
<td>National Institute for Clinical Excellence176</td>
<td></td>
</tr>
<tr>
<td>Birmaher13</td>
<td>Hughes173</td>
<td>New Zealand Guidelines Group189</td>
<td></td>
</tr>
<tr>
<td>Gallagher175</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health Specialists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birmaher13</td>
<td></td>
<td>Anderson177</td>
<td></td>
</tr>
<tr>
<td>Gallagher176</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Allied Mental Health Disciplines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birmaher13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPG = clinical practice guidelines; MDD = major depressive disorder; MH = mental health

Inadequate Response

Only two CPGs provided definitions of inadequate response and this was characterized as failure of remission over a period of at least 2 weeks and less than 2 months, with no or very few depressive symptoms using a children's global assessment scale/interviews13 or as failure to have a significant level of improvement from 4 to 6 weeks.189

Quality Assessment of CPGs for Adolescents

Table 35 shows the domain scores for the AGREE II ratings of the CPGs. One guideline rated poorly across three domains (Domains 3 to 5) (range 0 to 33 percent).175 All CPGs for adolescents scored high for scope and purpose” (Domain 1) (range 89 to 100 percent).

The remaining domains showed highly varying scores from four to 97 percent in the stakeholder involvement (Domain 2), and the views of the patients and public were sought in only two CPG173,176 (score six or greater). For the domain of rigour of development (Domain 3), scores varied from 21 to 92 percent; only one CPG176 indicated a process for updating the guideline. There was moderate variability observed in the clarity of presentation (Domain 4) (range 33 to 97 percent); this domain evaluated whether the recommendations were clearly presented and would suggest that most did this well.

When considering the applicability domain (Domain 5), scores varied from zero to 77 percent; the majority of CPGs scored poorly for two criteria within this domain: 1) consideration of potential resource implications of applying their recommendations; and, 2) presenting monitoring or auditing criteria. For the domain regarding editorial independence (Domain 6), scores were highly variable and ranged from 13 to 100 percent; in particular, the competing interests of the guideline development group were not consistently recorded.

As expected, the CPGs for adolescents had varying methods to establish the strength of the evidence and they could not be compared with each other. Similar to adult rating systems, most CPGs used grading systems that included aspects of study design (e.g., RCT), number of studies, or confidence of treatment; most included a level that reflected consensus or expert opinion for some recommendations.
Table 35. The AGREE II ratings for the 6 domains in CPG applicable to adolescents

<table>
<thead>
<tr>
<th>Year</th>
<th>Organization</th>
<th>Scope and Purpose (Domain 1)</th>
<th>Stakeholder Involvement (Domain 2)</th>
<th>Rigor of Development (Domain 3)</th>
<th>Clarity of Presentation (Domain 4)</th>
<th>Applicability (Domain 5)</th>
<th>Editorial Independence (Domain 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>United States</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuckerbrot 2009</td>
<td>American Academy of Pediatrics</td>
<td>91.67</td>
<td>61.11</td>
<td>79.17</td>
<td>86.11</td>
<td>66.67</td>
<td>75.00</td>
</tr>
<tr>
<td>Cheung 2007</td>
<td>Guidelines for Adolescent Depression in Primary Care</td>
<td>100.00</td>
<td>63.89</td>
<td>81.25</td>
<td>80.56</td>
<td>22.92</td>
<td>50.00</td>
</tr>
<tr>
<td>U.S. Preventive Services 2009</td>
<td>U.S. Preventive Services Task Force</td>
<td>88.89</td>
<td>58.33</td>
<td>34.38</td>
<td>33.33</td>
<td>33.33</td>
<td>20.83</td>
</tr>
<tr>
<td>Hughes 2007</td>
<td>Texas Department of State Health Services</td>
<td>100.00</td>
<td>91.67</td>
<td>47.92</td>
<td>91.67</td>
<td>37.50</td>
<td>62.50</td>
</tr>
<tr>
<td>Birmaher 2007</td>
<td>American Academy of Child and Adolescent Psychiatry</td>
<td>91.67</td>
<td>55.56</td>
<td>65.63</td>
<td>80.56</td>
<td>37.50</td>
<td>16.67</td>
</tr>
<tr>
<td>Gallagher 2005</td>
<td></td>
<td>100.00</td>
<td>41.67</td>
<td>21.88</td>
<td>33.33</td>
<td>0.00</td>
<td>66.67</td>
</tr>
<tr>
<td><strong>United Kingdom</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 2008</td>
<td>British Association for Psychopharmacology</td>
<td>91.67</td>
<td>58.33</td>
<td>72.92</td>
<td>91.67</td>
<td>2.08</td>
<td>12.50</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence 2005</td>
<td>National Institute for Clinical Excellence</td>
<td>100.00</td>
<td>97.22</td>
<td>92.71</td>
<td>97.22</td>
<td>77.08</td>
<td>91.67</td>
</tr>
<tr>
<td><strong>Australia New Zealand</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Zealand Guidelines Group 2008</td>
<td>Ministry of Health &amp; New Zealand Guidelines Group</td>
<td>100.00</td>
<td>66.67</td>
<td>69.79</td>
<td>88.89</td>
<td>39.58</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NR = not reported

Recommendations of CPG for Adolescents

Three of eight CPGs for adolescents did not provide any specific recommendations for adolescents who had failed to respond to previous treatment. One component of a CPG from the GLAD-PC focused only on identification and initial management. One CPG focused only on psychotherapy interventions and did not provide any recommendations specific to those who failed previous treatment. Another CPG from the USPSTF focused primarily on recommendations for screening and initial management. One guideline indicates that there is lack of evidence for the management of next steps of treatment for adolescents and provides no further indications.

Two CPG provided recommendations following failure of psychological interventions. One CPG that evaluated treatment for MDD in both adult and adolescent populations, directed primary care practitioners to refer to secondary mental health services following lack of substantial improvement after six to eight weeks of supportive and psychological therapies. Similarly, the recommendation was to seek adolescent psychiatric consultation if the use of an antidepressant was desired. Two CPGs provided recommendations for patients who had
failed to respond to psychotherapy or had more complicated depressions; failure to respond to pharmacological treatment was not clarified for mild depression and recommended only for moderate to severe MDD.

Table 36 shows the proposed treatment options for adolescents with MDD. Three CPGs\textsuperscript{13,173,194} note the lack of evidence for adolescents, but cite adult evidence as the rationale for the treatment strategy of switching and augmentation in particular. One CPG makes clear recommendations to avoid the use of paroxetine and venlaxafine in adolescents 12 to 18 years of age.\textsuperscript{176}
Table 36. Recommendations for treatment in CPGs that identified strategies for those that failed response (n=5) in adolescents

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combined Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Interval (weeks)</strong></td>
<td><strong>Dose or Duration Change</strong></td>
</tr>
<tr>
<td><strong>United States</strong></td>
<td></td>
</tr>
<tr>
<td>Cheung 2007[174]</td>
<td>6-8</td>
</tr>
<tr>
<td>Hughes 2007[173]</td>
<td>NS</td>
</tr>
<tr>
<td>Birmaer 2007[13]</td>
<td>2 – 8</td>
</tr>
<tr>
<td><strong>United Kingdom</strong></td>
<td></td>
</tr>
<tr>
<td>National Institute for Clinical Excellence 2005[175]</td>
<td></td>
</tr>
<tr>
<td><strong>New Zealand/Australia</strong></td>
<td></td>
</tr>
<tr>
<td>Dudley 2008[194]</td>
<td>4</td>
</tr>
</tbody>
</table>

AD = antidepressant; BUP = bupropion; CBT = cognitive behavioral therapy; CIT = citalopram; CON = consultation with mental health specialist; DUL = Duloxetine; ESC = escitalopram; FLX = fluoxetine; IPT = Interpersonal therapy; LI = lithium; MIR = Mirtazapine; NS = Not significant; PAX = paroxetine; PSY = Psychotherapy; SER = sertraline; SSRI = selective serotonin reuptake inhibitors; VEN = venlafaxine; T3 = Tri-iodothyronine

* not recommended for preadolescents.

⁰ not ideally recommended but can be considered.

X – detailed as a possible treatment approach for those with inadequate response.

# Must have failed two SSRI and augmentation precedes switch to nonSSRI.

ECT if pharmacological treatment fails or depression is severe.

% Considered only for severe or psychotic cases.

The time interval indicates the number of weeks following the first-line therapy attempt to initiate new treatment strategy.
Discussion

Overview

Pharmacological agents are one of several treatment modalities used to treat major depressive disorder (MDD). One of the most frequently utilized classes of antidepressant medications is the selective serotonin reuptake inhibitors (SSRIs). However, the rates of treatment response following first-line treatment with SSRIs is moderate, varying from 40 to 60 percent; remission rates may vary from 30 to 45 percent.\(^1\) This CER has summarized the evidence for management of patients subsequent to a trial of an SSRI that did not result in an adequate response.

KQ1. Among adults and adolescents with Major Depressive Disorder, Dysthymia, and Subsyndromal Depression, who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

KQ1a. How does the efficacy/effectiveness vary between the different monotherapies and combined therapies?

Adults

This CER has identified and shown that the evidence comparing varying treatment strategies following failed response to an SSRI are of low quality or are insufficient overall. The evidence for single treatments (monotherapies) compared either with the same or lower doses, switching to different agents, or augmentation or combination therapies following inadequate response to SSRIs is limited with respect to the number of studies, the agents evaluated, and their methodological quality. As such, many relatively straightforward clinical questions remain to be addressed. When patients are being treated with an antidepressant and are not improving, the first step is often to ‘optimize’ the treatment, most often defined as an adequate dose for an adequate duration of time; there is, however, no consensus on exactly how long a patient should be treated with a medication before there is a decision made that the response has been inadequate.

The issue of determining what defines an inadequate trial of an SSRI is therefore not straightforward; while most studies used adequate doses of medications (as defined when the medication receives an indication from a regulatory authority) the duration of treatment with the SSRI prior to a judgment is made regarding the inadequacy of the response, was highly variable across the trials that were reviewed. The duration of treatment with an SSRI prior to the determination of an inadequate response ranged from a mean of approximately 4 to 12 weeks. Although adequate doses may be those defined in product monographs, there has been uncertainty regarding the maximal dose to which many common antidepressants should be prescribed. Despite this, a survey conducted a decade ago suggested that the preferred intervention of clinicians following inadequate response to an SSRI was a dose increase. Only three studies have examined whether an increase in dose in this population is associated with a comparable probability of response or remission relative to maintaining standard doses (either as a continuation of the original SSRI or as switch to a new antidepressant); direct comparison of
dose changes relative to selecting another strategy, such as a medication switch or an add-on therapy, was not evaluated in the eligible studies within this review.

Once a decision is made to move beyond optimizing the SSRI regimen, clinicians have several options available, including switching to a new medication (either of the same antidepressant class or a different class), adding a second antidepressant, or adding another agent that itself might not be recognized as an antidepressant in monotherapy. In recent years, the line between ‘augmentation’ agents and ‘antidepressant’ medications has been questioned, leading some investigators to suggest that the standard terminologies of ‘combination’ therapy (to refer to multiple antidepressant treatments, either pharmacological or other, being used at the same time) and ‘augmentation’ therapy (to refer to an antidepressant used in conjunction with another nonantidepressant therapy) should be collapsed and called ‘add-on’ therapy. Regardless of preferences for nomenclature, this review has highlighted that there is an extremely limited evidence base to support clinical decisionmaking about any of these strategies or which agents to select. The variation amongst CPGs reflects this uncertainty.

A common treatment approach following inadequate response to first treatment is to switch medications. Despite the large cohort of patients in the STAR*D trial, there remains insufficient or low quality evidence to determine whether a patient who elects to have a medication switch following an inadequate response to one SSRI can be switched to another SSRI with equal likelihood of response or remission compared to a switch to a medication from another class. The STAR*D trial suggested that this might be the case, at least when comparing sertraline, venlafaxine, and bupropion, but given the frequency with which this question arises in clinical practice, a more substantive evidentiary base on which to make this decision appears warranted. Another common clinical issue following inadequate treatment response is whether to add a medication, either another antidepressant or a nonantidepressant agent, traditionally called an augmenting agent. Adding a second antidepressant to an SSRI is not uncommon in clinical practice, particularly if patients have had a partial response (at least 20 percent improvement).

Altamura and colleagues82,83 have compared intravenous citalopram with intravenous clomipramine following inadequate response to SSRIs, but these trials were preliminary and the short term use of intravenous medication does not address the more typical situation in which patients have a second oral medication added to the SSRI.

Traditional augmentation strategies comprised the bulk of studies meeting criteria for inclusion in this review. Most trials investigated whether adding a new agent to ongoing SSRI treatment was preferable to adding a placebo to ongoing SSRI treatment. Therefore, in most instances what was compared was monotherapy with the initial SSRI against cotherapy with the original SSRI and a new agent. Although the majority of studies fell into this category, there are a limited number of studies for any particular augmenting agent, limiting the strength of the results. The array of agents studied meant that it was difficult to make informed decisions regarding specific classes of medications. Additionally, there are very few studies that examined augmentation compared with switching strategies, which is a clinically relevant question. That is, many clinicians would likely find it helpful to understand the conditions under which it is preferable to add a second treatment rather than switch medications. At least one previous report suggested that clinicians tend to switch medications when there has been minimal response to the treatment and augment when there has been partial response, but whether this approach results in optimal outcomes is not known.195

The use of atypical antipsychotics has recently gained prominence in the clinical community. Olanzapine was one of the first atypical antipsychotic medications evaluated. Other atypical
antipsychotic medications have since been studied as potential add-on, and even monotherapy, treatments for MDD. Aripiprazole has been studied as an add-on therapy for patients not responding to antidepressant medications, but the results are not reported in these publications, as SSRI-specific subgroup data are reported only as mean change scores rather than remission and response rates. In the United States, this agent now has an indication as an add-on therapy for patients who do not have adequate response to antidepressant treatment. Similarly, quetiapine, another atypical antipsychotic medication, has been studied as add-on therapy in MDD, but the studies were not restricted to SSRI treated patients and the data could not be disaggregated in order to examine the effectiveness of this approach for patients treated only with SSRIs. A recent pooled analysis not eligible for our review due to publication date, reports showing statistically significant differences in mean scores for the SSRI subgroup favoring quetiapine.

A meta-analysis examined the role of atypical antipsychotic medications as add-on therapies in MDD. The authors reported that the mean odds ratios (ORs) were similar for the various atypical agents studied (olanzapine, quetiapine, risperidone, and aripiprazole); they further reported that they could not appreciate that trial duration or method of establishing treatment resistance influenced the pattern or magnitude of the reported results. The OR reported for response in that meta-analysis (OR 1.69, 95% CI 1.46 to 1.59) is comparable to the relative risk (RR) in the risperidone trial by Mahmoud and colleagues (RR 1.86, 95% CI 1.16 to 2.96), and more modest than the preliminary results presented by Shelton and colleagues for olanzapine in combination with fluoxetine (RR 13.0, 95% CI 0.83 to 203.0).

Although lithium was once described as the single agent with the most extensive evidence base for use as an augmenting agent in MDD, surveys suggested that it did not have wide uptake in the United States as an agent for treating people with unipolar depression. The results of lithium trials in this evidence review do not support its position as a leading augmentation strategy for this population. We recognize that the trials examined here represent only the portion of lithium trials in which patients were treated with SSRIs initially (meeting the criteria for inclusion in this review). Lithium may, however, have anti-suicide properties or other features that may make it attractive as an add-on agent in some patients with MDD, such as its low potential to induce a mood switch or cycling in depressed patients with strong genetic vulnerability to bipolar disorder.

There is an extremely limited evidentiary base on which to make conclusions regarding the relative efficacies of various combination treatment approaches for patient with an inadequate response to an SSRI. One treatment strategy is to use a combination of treatment modalities, such as a medication in combination with cognitive behavioral therapy (CBT). The STAR*D trial attempted to measure the value of both CBT as monotherapy and CBT in combination with ongoing citalopram treatment, but the number of patients electing CBT or agreeing to the possibility of being randomized to CBT was small compared to the overall sample size, and this limits conclusions that can be drawn about CBT from the STAR*D trial. A number of issues related to the provision of CBT in the STAR*D trial have been suggested to account for the relatively small number of patients who found CBT an acceptable option, and these may have limited the generalizability of the patients willing to enter that arm. Another eligible trial of a modified cognitive therapy administered to patients as an augmenting agent following nonresponse to antidepressant medication, found that psychotherapy was not different to next step pharmacotherapies that were described to have “closely paralleled those in the STAR*D study.” A relevant question for clinicians is whether patients who do not have an adequate
response to treatment with an antidepressant would do better with an additional medical or with a talk therapy; studies to date do not provide evidence that there are reliable differences in the expected outcomes between these approaches. A caveat to that statement, however, is that patients in both STAR*D and the recent REVAMP trial had many past episodes of depression and it is therefore unknown whether younger patients or those earlier in their course of illness would be more likely to benefit from the addition of CBT than the more chronic group. The TORDIA trial of adolescents with depression who received CBT in combination with medication suggested that this combination might be beneficial in those with a low past illness burden.

A large number of studies included a portion of patients treated with SSRIs and a portion treated with other antidepressant medications. Response and remission rates were not reported as a function of baseline therapy for most studies and although there was a systematic process for contacting authors of the studies, very few were able to provide response and remission data for the subgroup of patients treated with SSRIs. Even registration trials of new add-on treatments for patients not responding to an antidepressant medication have not examined whether the add-on agent is equally effective when added to a range of antidepressant classes. This resulted in the exclusion of a large number of studies containing relevant data because the data for SSRI treated patients could not be disaggregated from those treated with other antidepressants. There appears to be an assumption amongst investigators in this field that response and remission will be comparable regardless of the class of background medication. We are not aware of clinical or neurobiological data to convincingly support this assumption and we suggest that perhaps the assumption should be revisited. It is likely that the major disincentive to examining the effectiveness of various add-on therapies as a function of the antidepressant class used as cotherapy is that it will add to required sample sizes. It is possible that if extant studies were examined by disaggregating the various antidepressants employed as the primary treatment, that a preliminary investigation of whether add-on treatments are equally effective for all antidepressant classes could be conducted.

Depressive symptoms that do not meet full DSM criteria for a major depressive episode can be persistent and disabling. The DSM-IV has provided classification for dysthymia, but there is little evidence that dysthymia is distinct from subthreshold depressive symptoms apart from the extended duration of symptoms required for the diagnosis of dysthymia. The PROSPECT trial evaluated treatment of subthreshold symptoms in the elderly, and combined patients with subsyndromal depression (two symptoms), dysthymia, and minor depression as a single group. It would be useful for investigators to expand the evidence base examining whether distinctions between these subthreshold groups are important. It would also be useful for future treatment studies if a consensus could be reached regarding how to define treatment response or nonresponse when few symptoms are present at baseline.

Finally, the majority of studies did not state an intention to evaluate equivalency, noninferiority, or superiority relative to the standard treatment. Even if the trials had attempted to establish these differences, there are several challenges that need to be considered. The first challenge is specifying a priori the margins for defining equivalence, noninferiority, and superiority. There is a need to engage in consensus work to establish acceptable boundaries for these margins. Following this, appropriate power and statistical analyses to establish the equivalence, noninferiority, or superiority also need to be adequately reported. Additionally, an underlying assumption to such trial analyses, is that the standard treatment is efficacious. This assumption is problematic in those studies where one arm of the trial is a continuation of the
same intervention to which failed response is established. Similarly, studies that switch subjects to new treatments as the standard arm also challenge the assumption of efficacy.

Adolescents

Only three trials were identified that were of relevance to the adolescent population. The subset of relevant patients could not be extracted from one study (TADS), leaving two studies of children and adolescents that addressed the question of next line treatment for young people who have not had an adequate response to an SSRI. The TORDIA study appears to emphasize the role for CBT in treating youth. Results continue to emerge from the TORDIA trial and will likely provide further information describing the effective components of care for adolescents who have treatment resistant depression. The single trial evaluating dose escalation in children and adolescents would suggest that a dose increase did not show any significant differences in either outcomes of benefit or harm; however, this trial was not adequately powered. While the TORDIA trial represents a major advance in the recognition of the need to have data on second-line treatment approaches for adolescents with MDD, much more work is required to determine the most effective ways to optimize short- and long-term outcomes for adolescents with depression. The apparent benefit of CBT in combination with medication that was observed in the TORDIA trial was not similarly apparent in either the STAR*D or REVAMP trials. The TORDIA trial explicitly states that almost three in four patients were receiving their first treatment for MDD, while the STAR*D participants had a much higher average burden of illness, and the REVAMP participants were specifically chosen to have chronic depression. This raises the question of whether the effectiveness of CBT is determined in part by the illness history and burden of participants; it has been suggested that this might be the case for CBT in patients with bipolar disorder and is worthy of further investigation in unipolar depression. Access to CBT is limited in many jurisdictions, and as such, clinicians may choose to reserve the therapy for those who are in a stage of illness where there is a reasonable probability that it will be associated with superior results than other, more accessible, treatment modalities.

KQ2. What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

It is difficult to summarize any specific trend observed for harms in adults across all the different interventions in the eligible studies within this CER. In general, the types of the events reported were consistent with the use of antidepressants and these were generally classified as mild and relatively transient. The findings from this CER have shown that most treatment strategies show no relative differences and that either strategy (the standard or comparator) are likely of modest or uncertain benefit. In this context, evaluation of the harms takes on greater importance. That is, if there is no meaningful difference in the potential outcomes of benefit, the margins between benefits and harms become narrower. Given that many of the treatments that were evaluated likely have no difference (or are potentially equivalent), evaluation of the harms profile also takes on a greater importance in judging the relative efficacy of the two interventions. However, the limitations observed in collecting and reporting harms across the studies constrains the judgments made regarding the margin of difference between harms and benefits and the relative differences in safety profiles of likely equivalent treatments. The inability to distinguish if the studies did not measure these harms, rather simply not reporting them (either because no events occurred or they occurred at the lowest frequencies) makes rating
strength of evidence (SOE) problematic. We considered the measurement of suicidality critical, and therefore necessary for all studies, given the potential of a serious event in MDD and with most treatment approaches. The atypical antipsychotic medications carry a substantial burden of short- and long-term side effects, along with a need for routine metabolic monitoring. Other augmentation agents, such as lithium and tri-iodothyronine, also have short- and long-term harms associated and also require the need for routine bloodwork and possibly other monitoring. Because the short- or long-term harms have not been systematically compared across agents, it is not possible to make a relative determination regarding the potential for harms between agents added as a second-line treatment. There are other potential harms, such as the lethality of a medication in overdose, that are relevant to prescribing physicians but are not routinely captured in clinical trials.

All but one study\textsuperscript{112} reported some aspect of safety and tolerability, and similarly, only one study was partially designed to evaluate harms as a primary outcome.\textsuperscript{114} No observational studies evaluating inadequate response to SSRIs were eligible for this review; as such, potentially long-term consequences of these treatment strategies (e.g., increasing the dose or adding an augmenting agent) typically evaluated in such studies are therefore not known. Recognizing that from a statistical perspective, it may be difficult to evaluate statistical differences when event rates are low, we found that the majority of studies did not undertake such tests when comparing differences between groups. Thus, establishing clinically important differences in harms profiles (largely reported as frequencies) is based mainly on judgements.

Rates of discontinuation due to adverse events were variable. The duration of a study can have an important influence on the reported rate of discontinuation. In studies with open-label prospective failure components, the number of patients who had adverse events and did not proceed to the next phase, were not consistently reported. In studies with historical failure, the proportion of subjects who had experienced inadequacy of response due to intolerance because of harms, was not sufficiently detailed. Some studies excluded subjects with any history of drug reactions. Thus, intolerance was not distinguished from inadequate response in these retrospective studies. Disentangling this issue may prove to be helpful in understanding who may achieve a more favorable response in second-line treatment approaches.

Washout periods were included in very few study protocols. For interventions with a switch to new interventions, this may be problematic as early side effects from these new treatments may reflect symptoms related to withdrawal from the previous SSRI or medication rather than reflecting the harms associated with the new treatment.

The method of assessing adverse events differed greatly among studies, with a limited number utilizing standardized scales specific to harms, or reporting adequate details about the protocols and methods used to assess harms. \textit{A priori} definitions of serious or severe harms were consistently not specified within eligible studies. Details regarding the qualifications of the assessor or how harms were decided to be linked to the treatment were almost always lacking. Both of these factors suggest the high risk of bias due to misclassification. Future clinical trials should conform to CONSORT reporting standards for harms.\textsuperscript{207}

The two studies evaluating harms in adolescents used standardized harms reporting instruments and provided details about the frequency of assessment, assessor characteristics and sufficient details about how the harms were collected to allow for replication of the methods. This suggests a higher sensitivity for adequate collection and reporting of harms in this younger population. However, the potential for long-term adverse events within this population is not known, as no observational studies specific to the failed SSRI group were identified.
KQ3. How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, age, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)? These subgroups will be considered with respect to the different interventions.

There are seven studies in adults and one for adolescents with MDD that undertook stratified or subgroup analyses evaluating factors that may impact treatment outcomes. The findings for baseline severity are inconsistent, with two studies suggesting no impact and three showing that higher baseline scores were linked to a greater change in scores, or that those with more severe depression are less likely to achieve remission. It is important to note that many studies excluded subjects with psychiatric comorbidities, particularly subjects with anxiety disorders, bipolar disorder, or depression with psychotic features. The STAR*D cohort showed that those with concurrent anxiety related psychiatric comorbidities were less likely to achieve remission, and that the various treatments did not benefit the anxious group any differently. No clear trend emerges for previous history of failure, age, gender, or race. From a clinical perspective, all of these factors have face validity as potentially important treatment modifiers. One could argue that there is a greater need to evaluate these characteristics as potential prognostic factors in populations who have failed to respond. The link with risk factors for predicting failed initial response (first episode) may provide important information for subsequent management of these patient populations.

Neither of the two studies evaluating children and adolescents assess specific subgroups with respect to age or severity. An analysis of the TORDIA trial on predictors of treatment response showed that milder depression, less family conflict, and absence of suicidal behavior were associated with greater likelihood of a positive treatment response at 12 weeks. There was some evidence that there was a differential response to combined treatment in adolescents with a history of sexual and physical abuse; this suggests that specialized clinical approaches may need to be considered in this subgroup of patients.

KQ4. What is the range of recommended clinical actions following the failure of one adequate course of an SSRI based on current clinical practice guidelines published between 2004 and April 2011?

To our knowledge, a comparison of CPGs on managing MDD, dysthymia, and subsyndromal depression in general, much less for those who failed to respond to antidepressant treatment, has not yet been undertaken. This CER evaluated 27 CPGs published in English, limited to those applicable in the national context or from large national professional associations. Seven CPG that were specific only to adolescents, 18 CPG to adults alone, and two were applicable to both adults and adolescents. All guidelines were applicable to patients with MDD but only four CPGs included recommendations for patients with dysthymia and subsyndromal depression. None of the four guidelines with recommendations for this subgroup provided recommendations for those who had failed to respond to previous treatment, possibly reflecting a lack of consensus for treatment in general or recognition for management of this subgroup of depressive disorders. This also raises the issue of interpreting “failed” response in a group for which the range of change is much smaller (fewer symptoms at baseline) relative to those with MDD for which the outcomes were originally designed.
From these CPGs, four did not provide any recommendations for subjects who had an inadequate response. These guidelines were not excluded, as our interest was in identifying the relative proportion of guidelines that did not address the population of interest.

From 18 CPGs in adults, the majority did not report any specific definitions for adequate response or remission within the guideline. For CPGs that did report a formal definition of inadequate response, only two CPGs provided clear indications for differential treatment strategies for those with partial versus nonresponse. This would suggest that the clinical and research community may require both consensus work and knowledge translation strategies to establish standardized definitions for failed or inadequate response. Concomitant to this issue is work to either select a single instrument or to allow for cross referencing between instruments. It is not clear that a 50 percent change in response relative to baseline on the PHQ-9 is similar to a 50 percent change on the HAMD-31.

Evaluation with the AGREE II instrument showed very high variation in the domains of rigour of development, applicability, and editorial independence. This was amplified for the guidance targeted at groups that had inadequate responses to initial treatment. This AGREE II criterion assessed whether the recommendations were clear and unambiguous, such that treatment options were distinctly presented, and key recommendations easily identifiable. The wide variation in strategies recommended across CPGs would seem to match the insufficiency of the evidence shown in our review for many treatment strategies. Although some CPGs clearly stated the limitations of the evidence, others did not and often selectively reported findings from studies to match the recommended course of action. The uncertainty of the evidence needs to be better highlighted in these CPGs.

The operational definition of CPGs is “systematically developed statements about specific clinical problems intended to assist practitioners and patients in making decisions about appropriate health care” presented some challenges. Our review excluded algorithms, which aim to provide guidance with regard to treatment strategies, methods of implementation, and treatment steps. Algorithms are often included in CPGs, but are not in and of themselves a guideline and the process of development may be preceded by a review of the evidence. The use of algorithms in clinical practice may be as prevalent as the use of CPGs, for example, the Texus Algorithm for MDD. Future developers of CPGs may wish to develop algorithms that can be incorporated into their guidelines that are evidence-based or at the least identify that they represent best practices.

Most CPGs failed to note or include any patient representation (a key stakeholder) in the development process. Although the CPGs generally rated as acceptable (higher scores) for attempting to link the evidence with the recommendations, the clinical sensibility of these treatment strategies are not addressed by the AGREE II. A variety of grading systems were used and comparison across different CPGs was problematic. The lack of clear guidance for some treatment options further compounded interpretations across guidelines.

The recommendations for most CPGs were stated broadly (switch or augment) and the link between the presentation of the evidence and the specific treatment recommendations was problematic in most CPGs. Few provided clear specification that there was insufficient evidence; rather, any available evidence was summarized with valuations of the strength of the evidence. For adults, the majority of CPGs did not indicate specific types of antidepressants when recommending switching to monotherapy strategies. Increases in the dose and duration of treatment was frequently recommended but the treatment interval or change in dose was not specified. When combined therapy was recommended there was a greater tendency to specify the
medication to be added. However, there was great variability across CPGs in the augmenting agents recommended. The lack of specificity and the relatively high degree of variability is most likely related to the limitations of the evidentiary base.

Guidelines for adolescents scored equally poorly on the AGREE II domain for clarity of presentation of the recommendations. Three of seven guidelines cited adult evidence to justify recommendations for some pharmacological strategies, particularly the use of augmentation agents. Only two CPGs provided definitions of inadequate response. Two guidelines considered failure following nonpharmacological interventions rather than inadequate response to antidepressants, which may reflect a preferential tendency to adopt nonpharmacological strategies in youth. In general, the CPGs for adolescents had a greater tendency to specify the medications to consider for both monotherapy and combined therapy. However, all noted the limitations of the evidence applicable to adolescents.

**Applicability**

The study populations in the eligible literature were relatively homogenous but were limited to predominately white or Caucasian women within a relatively narrow age range, often with mild to moderate depression. Additionally, there was a tendency to exclude patients who had medical and psychiatric comorbidities. The majority of the participants in the studies often had greater than two past episodes and high numbers (greater than two) past treatment failures on antidepressants. As such, the study subjects represent a narrow spectrum of patients with MDD who are likely to fail to respond when presenting to clinicians in primary care settings. As noted previously, there were few studies evaluating patients with dysthymia and subsyndromal depression, or in children and adolescents.

The dose range of many of the SSRIs and other antidepressants were within standard ranges used as monotherapy or as add-on agents. However, there was some variability in dosing for some augmentation agents and a general lack of rationale for the selected doses of these agents. There are limited data confirming that the doses selected for nonantidepressant augmentation agents reflect the optimum doses of those medications, in the context of augmenting another agent in a person with MDD. In some instances, the rigour of the nonpharmacological treatments may not be consistent with those seen in outpatient settings that patients might access. For example, within the TORDIA trial, the type of CBT was intensive and had high fidelity, but it is not clear if accessing therapists with expertise in working with adolescents is feasible in all jurisdictions. The variation in treatment duration across studies is potentially problematic; this may reflect a lack of consensus as to what constitutes an adequate treatment duration. The assumption has been that treatment duration with combined pharmacological agents are similar to those for antidepressants (a minimum of 4 to 6 weeks).

There is the additional problem of regulatory approval for many of the drugs used as augmenting agents. Some of these drugs do not have any approval by the U.S. Food and Drug Administration (Agomelatine (Valdoxan), Reboxetine (Edronax, Vestra), Norvale (Mianserin, Bolvidon, Tolvan), and many others do not have approval as augmenting agents, suggesting their off label use.

The outcomes used in most studies (for example, the MADRS or HAMD) are clinician administered; fewer studies used self-report instruments (for example, the QID-SR16 or the PHQ-9). The feasibility of using such instruments in primary care is a consideration that is recognized in the clinical literature. Most of these studies were undertaken in outpatient mental health or primary care settings and are therefore applicable to the settings to which the
majority of patients will be seen by practitioners. Conversely, the findings of this review may not be applicable to patients in different settings such as inpatient or specialized psychiatric contexts. However, we note that characteristics of inpatient and outpatient settings differ within health care systems and countries; it is conceivable that important patient characteristics (e.g., severity, duration) may not actually differ between some inpatient and outpatient settings.

There are some special considerations with respect to the monitoring of harms in primary care settings. Although we found the majority of studies did not provide sufficient detail regarding the collection of harms, there is a tendency to monitor harms more rigorously and with the use of standardized instruments in the studies. For example, the TORDIA trial had employed rigorous methods for monitoring harms (for example, weekly monitoring for those displaying any adverse events) and this may be difficult in replicate primary care settings.

Comparative Effectiveness Review Limitations

This CER has several constraints in its methodology in the context of the literature search. Although over 40,000 citations were screened, the citations were limited to those published in the English language. In addition, the search was limited to publications from 1980 forward, as SSRIs were not in use prior to this time. In consultation with the TEP and partners, issues around predictors of response were considered and it was recognized that the scope of the review was sufficiently large to prohibit evaluation of predictors of response.

We identified a large number of studies that had patients who had failed to respond to a variety of antidepressants; those studies that clearly included only 100 percent of patients who failed on a non-SSRI, or those who had failed on combination therapies prior to entry into the study, were excluded. However, there was a subset of studies that had some proportion who may have failed treatment on an SSRI prior to entry. Attempts were made to contact all authors (n=167 studies) of these studies, who were asked to provide subgroup data specific to the SSRI failed group. Some authors declared that they could not provide us with stratified analyses and these studies were excluded. The contact information for some authors was incorrect, and several attempts to find information related to the publication investigators was made; for some of these, direct contact with the authors was not successful and these studies were excluded as well. Some of the authors did not respond to emails, and after two attempts we excluded these publications as well. A limited number of authors provided us with some stratified results for outcomes and we acknowledge that some of the findings from these stratified analyses may be compromised as the study designs were not such to ensure balance between the SSRI and non-SSRI failed subjects.

A search of the grey literature identified approximately 350 links to regulatory agency documentation, and 171 of these were directly related to drugs found within our eligible studies. The aim in searching these sources was to identify unpublished trials and for potential deviations for reporting of study findings. However, none of these sources provided additional information to identify unpublished trials and evaluate the potential for reporting biases; this was primarily limited by the population (previous failure to SSRI). Previous research specific to antidepressants has shown significant differences in the information reported to the FDA, relative to the same study publication in peer review journals.209 Our search of clinical trial registries identified that only 11 from 44 of our eligible studies (adults and adolescents) had been registered within the sources we were able to search.42,44,80,87-89,101,103-106,108-110,113,126,131,132,140,141 Moreover, the abbreviated information within the registry trials was not helpful in identifying selective reporting of outcomes or deviations to the stated protocols (for example, reporting
information on early phases of the trial or not detailing any subsequent protocol modifications). Trial registries are dependent on investigators to voluntarily update information and may not reflect the most updated source of trial protocol information.

**Summary/Conclusions**

KQ1. Among adults and adolescents with Major Depressive Disorder, Dysthymia, and Subsyndromal Depression, who are started on an SSRI and who are compliant with treatment but fail to improve either fully, partially, or have no response, what is the benefit (efficacy or effectiveness) of monotherapy and combined therapy?

KQ1a. How does the efficacy/effectiveness vary between the different monotherapies and combined therapies?

1. Studies in adults with MDD and an inadequate response to an SSRI included a preponderance of subjects with multiple past depressive episodes and multiple past unsuccessful treatment trials. The generalizability of these data to people with few past episodes of depression may be limited.

2. Studies in adults with MDD and an inadequate response to an SSRI included a high proportion of whites and women and tended to have an average patient age in the early forties.

3. Studies in adults examining treatment for a major depressive episode following inadequate response to an SSRI examined monotherapy compared with monotherapy, monotherapy with combination therapy or combinations of therapies. The majority of studies compared monotherapy (usually ongoing treatment with the initial SSRI) with a combination of therapies (usually ongoing treatment with the initial SSRI in addition to a nonantidepressant medication).

   a. The number of studies comparing single medications against each other (monotherapy compared with monotherapy) following an inadequate response to an SSRI is extremely limited. Extant studies are limited in type of agents utilized, sample sizes, and population characteristics. The extant data do not support a difference between various single agent therapies for the outcomes of response and remission.

      i. **Strength of Evidence:** There is insufficient evidence to evaluate the benefits of changing the dose, switching to a different SSRI, a nonSSRI antidepressant, a nonantidepressant medication, or a nonpharmacological treatment following an inadequate response to an SSRI. With respect to harms there is also insufficient evidence from the studies that were reviewed but the known differential adverse effect profiles amongst different drug categories may provide guidance in making a comparative benefit-risk assessment.

   b. The largest number of eligible studies examined monotherapy with combination therapy. The majority of studies compared outcomes following ongoing treatment with placebo added to the initial SSRI (the agent to which the subject had not responded by a defined time interval) with outcomes when an active agent was added to the initial SSRI.
i. Strength of Evidence: There is insufficient evidence to evaluate the benefits of ongoing monotherapy with an SSRI as opposed to combination treatment involving the addition of another antidepressant medication to the initial SSRI.

ii. Strength of Evidence: There is low grade evidence that comparable results are achieved following switch to an alternate antidepressant medication (monotherapy with a new antidepressant) when compared with adding a nonantidepressant treatment to the initial SSRI (traditional augmentation approach).

iii. Strength of Evidence: There is low grade evidence that adding an atypical antipsychotic medication to ongoing SSRI treatment is associated with higher response and remission rates compared with adding a placebo to ongoing SSRI treatment.

iv. Strength of Evidence: There is insufficient evidence for the benefit of other augmentation agents (buspirone, lithium, mianserin, other pharmacological agents, and psychological interventions).

c. Studies examining combinations of treatment were also extremely limited in number, types of medications, and homogeneity of populations. Extant data do not suggest that any specific combination of active treatments is different to another specific combination of treatments.

i. Strength of Evidence: There is insufficient evidence to evaluate the benefits or harms of specific combinations of treatments relative to alternative combinations.

4. Studies examining response and remission rates in children and adolescents to treatment subsequent to an inadequate SSRI response were extremely limited. Of three potential trials, data could only be extracted from two and one was a pilot study evaluating dose escalation. The TORDIA trial was of high quality and the results did not show a difference when monotherapy treatments were compared; a switch from the inadequate SSRI to another SSRI was associated with comparable outcomes to a switch to an SNRI. The trial did, however, report that combination therapy of a medication and CBT was superior to monotherapy with a medication.

a. Strength of evidence: There is low grade evidence to support the use of CBT in combination with an antidepressant following inadequate response to an SSRI for adolescents (age 12 to 18) with MDD.

5. Studies examining response and remission rates in patients specifically selected to have subsyndromal symptoms associated with inadequate response to SSRI were also extremely limited. Only one trial was eligible and that trial had metabolic parameters as the primary outcomes interest.

a. Strength of evidence: There is insufficient evidence to support the use of specific treatments for patients with subsyndromal symptoms following an inadequate response to SSRI medications.

6. Studies examining patients with dysthymia, but not MDD, and an inadequate response to an SSRI medication were extremely limited. Only one trial was eligible and that trial did not report a difference between treatment with paroxetine 40mg compared with paroxetine 20mg and amisulpride.

a. Strength of evidence: There is insufficient evidence to support the use of various treatment approaches for patients with dysthymia who have inadequate response to an SSRI.
KQ2. What are the harms of each of the monotherapies or combined therapies among these adults and adolescents? How do the harms compare across different interventions?

1. Harms for interventions used in both adults and adolescents with MDD who had failed to respond to an SSRI were derived from RCTs that evaluated treatment strategies in this population; no observational studies were eligible. A clear trend for harms was difficult to specify across the differing interventions in adults. Harms were evaluated and reported in a comprehensive and unbiased manner in the single study in adolescents.
2. Reporting and collecting of harms was problematic, particularly for predefining harms including serious and severe events and reporting total number of events per group in the studies with adults. The single study evaluating harms in adolescents provided high quality evidence for harms within this population when receiving pharmacological and psychological treatment.
3. The studies included were short term treatment trials. Harms that may not be apparent in short term clinical trials might emerge with long term use of agents. The relative potential for long term harms and monitoring burden of various agents was not evaluable in the short term treatment trials included here.

KQ3. How do these therapies compare in different populations (e.g., different depressive diagnoses, disease severity, ages, gender, racial and socioeconomic group, and medical or psychiatric comorbidities)?

1. There are a limited number of studies that have evaluated the impact of disease type, disease severity, previous comorbidities, age, gender, and race in the treatment of adults and adolescents who have failed to respond to an SSRI.
2. Only two studies have evaluated psychiatric comorbidities, and findings from the STAR*D cohort of level two adult patients would suggest that patients with anxiety related disorders (particularly anxious patients) are less likely to achieve remission.
3. There is high quality evidence from the TORDIA trial suggesting that mild depression, less family conflict, and the absence of suicidal behavior is associated with a greater likelihood of response in adolescents.

KQ4. What is the range of recommended clinical actions following the failure of one adequate course of an SSRI based on current clinical practice guidelines published between 2004 and April 2011?

1. The majority of clinical practice guidelines (CPGs) for adults were applicable to patients with MDD for outpatient and primary care settings. The majority of CPGs provided recommendations for patients who had failed previous treatments, but did not specify definitions of “inadequate response.”
2. No recommendations for persons with dysthymia or subsyndromal depression who had failed previous treatment were found in the limited number of CPGs that included this population.
3. Recommendations for monotherapy, including dose or interval changes, switching to a different SSRI, or a nonSSRI, were nonspecific as to the drug, interval, or dose change.
4. Recommendations for combination therapy tended to recommend specific types of antidepressants and augmenting agents. However, there was inconsistency across CPGs with regard to the types of augmenting agents to use.

**Future Research Recommendations**

Future research should attempt to incorporate the following recommendations for primary studies evaluating patients who have failed to respond to an SSRI:

**Population**

1. Include a broader representation of adult patients with respect to age (>50 and <40), gender (equal proportion of men), and ethnicity (increased proportion of non-white or non-Caucasian, or provide broader representation of all ethnic groups).
2. Include patients derived from primary care settings to incorporate a complete spectrum of participants who have failed to respond to an SSRI.
3. Give detailed specifications of how previous history of failed treatment was determined. The number of previous failures and, where possible, the antidepressant to which subjects had not responded and any factors associated with intolerance to antidepressants.
4. Specify previous mental health history including age at first diagnosis, length of current episode, and number of previous episodes at baseline.
5. Collect information about the presence of other medical and mental health comorbidities at baseline.
6. Collect information on the use of complimentary and alternative medicine (CAM) therapies that have the potential to confound and contaminate study interventions.

**Comparator and Study Design**

7. Determine treatment failure using a two-part study, the first part of which involves treating patients with SSRIs to prospectively determine failure. This confers methodological advantages in minimizing bias and allows the disentanglement of failure of response due to adverse events, compliance, or physiological response.
8. Specify the intent of the trial as attempting to establish equivalence, noninferiority, or superiority. Justification for the margin of inferiority or superiority should be detailed. Ideally, designing trials to establish superiority is preferred as this would assist clinicians in selecting treatment strategies.
9. Establish a sufficient sample size to show expected margins of difference between groups.
10. Establish a sufficient sample size to evaluate potentially important confounders such as age, gender, and baseline severity.
11. Consideration for possible additional studies that include subjects with dysthymia who have failed to respond to a previous SSRI. The validity of treating this diagnostic group needs to be considered, and if meriting treatment, then the evidence base should increase.
12. Consideration for possible additional studies with subjects with subsyndromal depression who have failed to respond to a previous SSRI. A clear definition of this subgroup (relative to dysthymia or minor depression) should be established. The validity of treating this diagnostic group needs to be considered, and if meriting treatment, then the evidence base should increase.
13. Increase the number of studies with children (ages 8 to 12) and adolescents (greater than 12 to 18 years). This patient population is increasing and needs to be adequately evaluated.

**Intervention**

14. Establish a clear rationale for the dose used for augmenting agents.
15. Establish efficacy across a range of antidepressant classes with new add-on treatments for patients not responding to an antidepressant medication. The assumption among investigators in this field is that response and remission will be comparable regardless of the class of background medication; the clinical or neurobiological data to support this assumption should be confirmed or revisited.
16. Evaluate the potential benefits of CAM therapies, either as monotherapy or augmenting agents.
17. The concomitant use of CAM therapies (co-interventions) that have the potential to confound interventions should be restricted or monitored (as are other pharmacological agents).
18. Long-term benefits and harms of various add-on agents will be apparent only with long-term followup. There are few studies examining the optimal duration of various treatment strategies beyond the achievement of remission. Future studies should examine whether the short-term benefits of various approaches are sustained and whether the harms of various approaches are acceptable.

**Outcomes**

20. Consider the inclusion of outcomes other than response or remission, but also include outcomes such as quality of life and speed of response.
21. Report the proportions of subjects who are classified as nonresponders (<20 percent) and partial responders (20 to 49 percent change from baseline) in addition to the sum of the proportion who did not achieve response.
22. Report the definition of adequate response and remission.
23. Conform to CONSORT\textsuperscript{207} reporting standards for harms. As such, severe and serious events (including suicidality) should be defined \textit{a priori} and the use of standardized instruments or terminology for reporting harms should be adopted. Long-term trials may be required to capture harms adequately.

**Other**

24. Studies with a sufficient sample size to explore these potential subgroups (age, gender, baseline severity, ethnicity, and type of depression) should be considered.
25. Register within clinical trial registries in order to evaluate the potential for publication bias and selective outcome reporting. Researchers should endeavor to regularly update information reported within these registries.

Future recommendations for the development of CPGs for adults, children, and adolescents should include the following:
1. A clear definition of inadequate response for both pharmacological and nonpharmacological treatments and standardized methods for establishing this in real world settings.

2. The addition of patient representation in the CPG development process.

3. Greater clarity with regards to recommended actions and the link with the evidence. Clinicians using the CPGs should be clear when evidence is insufficient.

4. Clear identification of when the recommendations are based on best practice recommendations (as when the evidentiary base is insufficient or weak) relative to when the evidence is sufficient.

5. The impact of contextual factors, such as practice setting (inpatient versus outpatient) or type of clinican (e.g., primary care practitioner, psychiatrist).
References


42. Brent D, Emslie G, Clarke G, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial. JAMA. 2008;299(8):901-13. PMID:18314433


119. Licht RW, Qvitzau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacol. 2002;161(2):143-51. PMID:11981594


158. Ravindran AV. If a patient does not respond to a full dose of fluvoxamine for at least 12 weeks, what alternatives should be considered? J Psychiatry Neurosci. 1998;23(2):136 PMID:9549254


Abbreviations

ACP  American College of Physicians
AHRQ  Agency for Healthcare Research and Quality
ASEX  Arizona Sexual Experience Scale
BDI  Beck Depression Inventory
CAM  complementary and alternative medicine
CANMAT  Canadian Network for Mood and Anxiety Treatments
CBT  cognitive behavioral therapy
CCT  controlled clinical trial
CDRS-R  Children’s Depression Rating Scale–Revised
CER  comparative effectiveness review
CGI  clinical global impressions
CPG  clinical practice guidelines
CYP 2D6  enzyme CYP 2D6
DBT  dialectical behavior therapy
DSHS  Department of State Health Services
DSM-IV  Diagnostic and Statistical Manual – 4th edition
ECT  electroconvulsive therapy
FDA  U.S. Food and Drug Administration
GLAD-PC  Guidelines for Adolescent Depression in Primary Care
HAMD  Hamilton Depression Rating Scale
HAMD-17/21/31 17 or 21 or 31 questions on the HAMD scale
HSRProj  Health Services Research Projects in Progress
IPT  interpersonal therapy
MADRS  Montgomery Asberg Depression Rating Scale
MDD  major depressive disorder
MDE  major depressive episode
mg/d  milligrams daily
NICE  National Institute of Clinical Excellence
PBO  placebo
PHQ-9  Patient Health Questionnaire 9 item
PICOT  Population, Intervention, Comparator, Outcome, Timeframe
QIDS-SR-16  Quick Inventory of Depressive Symptoms Self Report
QOL  quality of life
RCT  randomized controlled trial
rTMS  repetitive transcranial magnetic stimulation
SD  standard deviation
SNRI  Serotonin–norepinephrine reuptake inhibitors
SOE  strength of evidence
SSRI  selective serotonin reuptake inhibitors
STAR*D  Sequenced Treatment Alternatives to Relieve Depression
TADS  Treatment of Adolescents Study
TEP  technical expert panel
TORDIA  Treatment for Resistant Depression in Adolescents
UKU     Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale
U.S.    United States
USPSTF  United States Preventive Services Task Force
VNS     vagal nerve stimulation
WHO     World Health Organization
Appendix A. Search Strategy

OVID-Medline
April 13 2011
1. dysth*m.tw.
2. (subclinical adj2 depressi*).tw.
3. (subsyndromal adj2 depressi*).tw.
4. (subthreshold adj2 depressi*).tw.
5. (subdiagnostic adj2 depressi*).tw.
6. Depression/
7. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
8. or/1-7
9. serotonin uptake inhibitors/ or citalopram/ or fluoxetine/ or fluvoxamine/ or paroxetine/ or sertraline/
10. (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or seropram).mp.
11. (escitalopram or es citalopram or lexapro or cipralex or esertia).mp.
12. (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or lovan).mp.
13. (fluvoxamine or luvox or fevarin or faverin or dumyrox or favoxil or movox).mp.
14. (paroxetine or paxil or seroxat or sereupin or aropax or deroxat or rexetin or xetanor or paroxat).mp.
15. (sertraline or zoloft or lustral or serlain).mp.
16. ssri?.mp.
17. selective serotonin reuptake inhibit*.tw.
18. symbyax.mp.
19. or/9-18
20. Drug Resistance/
21. treatment failure/
22. Retreatment/
23. ((difficult or hard) adj3 treat).tw.
24. augment*.tw.
25. nonrespon*.tw.
26. non-respon*.tw.
27. switch*.tw.
28. ((insufficient or inadequate or incomplete) adj3 respon*).tw.
29. (ssri? adj3 (resist* or fail* or respon* or refractory)).tw.
30. (partial adj3 respon*).tw.
31. ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
32. ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
33. ((treatment resistant or refractory) adj3 depressi*).tw.
34. or/20-32
35. 8 and 34
36. 35 or 33
37. 8 and 19
38. 36 or 37
39. *depression/ or *depressive disorder/ or *depressive disorder, major/ or *dysthymic disorder/
40. or/1-5
41. 39 or 40
42. 5-Hydroxytryptophan/
43. phototherapy/
44. light therapy.tw.
45. exp Exercise/ae, th [Adverse Effects, Therapy]
46. exp Exercise Therapy/
47. exp Acupuncture Therapy/
48. exp Massage/
49. Relaxation Therapy/
50. exp vitamins/
51. Hypericum/
52. john* wort.tw.
53. deplin.tw.
54. methylfolate.tw.
55. Folic Acid/
56. S-Adenosylmethionine/
57. "SAM-e".tw.
58. exp Fatty Acids, Omega-3/
59. Cognitive Therapy/
60. Crocus/
61. Tryptophan/
62. exp Inositol/
63. or/42-62
64. 41 and 63
65. (harm? or adverse or "side effect?").tw.
66. (adjunct* or augment*).tw.
67. 65 or 66
68. 41 and 67
69. exp *antidepressive agents/ae, to [Adverse Drug Reaction, Drug Toxicity]
70. 68 or 69
71. 38 or 64 or 70
72. animals/ not (animals/ and humans/)
73. 71 not 72
74. (comment or editorial).pt.
75. 73 not 74
76. review.pt,sh.
77. 75 and 76
78. meta-analysis.pt,ti,ab,sh.
79. (meta anal$ or metaanal$).ti,ab,sh.
80. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
81. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
82. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
83. (medline or embase or cochrane).ti,ab.
84. or/81-83
85. review.pt,sh.
86. 84 and 85
87. 78 or 86 or 80 or 79
88. 75 and 87
89. 77 not 88
90. 75 not 89
91. limit 90 to yr="1980 -Current"
92. limit 91 to english language
93. 91 not 92

OVID-Embase
April 13 2011
1. depression/ or agitated depression/ or atypical depression/ or dysthymia/ or endogenous
depression/ or involutorial depression/ or major depression/ or masked depression/ or
melancholia/ or "mixed anxiety and depression"/ or "mixed depression and dementia"/ or organic
depression/ or reactive depression/ or recurrent brief depression/
2. dysthm*.tw.
3. (subclinical adj2 depressi*).tw.
4. (subsyndromal adj2 depressi*).tw.
5. (subthreshold adj2 depressi*).tw.
6. (subdiagnostic adj2 depressi*).tw.
7. or/1-6
8. serotonin uptake inhibitor/ or citalopram/ or escitalopram/ or fluoxetine/ or fluoxetine plus
olanzapine/ or fluvoxamine/ or paroxetine/ or sertraline/
9. ssri?.tw.
10. selective serotonin reuptake inhibit*.tw.
11. (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or serofram).mp.
12. (escitalopram or es citalopram or lexapro or cipralex or esertia).mp.
13. (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or
lovan).mp.
14. (fluvoxamine or luvox or fevarin or faverin or dumyrox or favoxil or movox).mp.
15. (paroxetine or paxil or seroxat or aropax or deroxat or rexetin or xetanor or
paroxat).mp.
16. (sertraline or zoloft or lustral or serlain).mp.
17. symbyax.mp.
18. or/8-17
19. Drug Resistance/
20. exp treatment failure/
21. Retreatment/
22. ((difficult or hard) adj3 treat).tw.
23. augment*.tw.
24. non-respon*.tw.
25. nonrespon*.tw.
26. switch*.tw.
27. ((insufficient or inadequate or incomplete) adj3 response).tw.
28. (ssri? adj3 (resist* or fail* or response or refractory)).tw.
29. (partial adj3 respon*).tw.
30. ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
31. ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
32. ((treatment resistant or refractory) adj3 depressi*).tw.
33. or/19-31
34. 7 and 33
35. 32 or 34
36. 7 and 18
37. 35 or 36
38. *depression/ or *agitated depression/ or *atypical depression/ or *dysthymia/ or
   *endogenous depression/ or *involutional depression/ or *major depression/ or *masked
depression/ or *melancholia/ or "mixed anxiety and depression"/ or "mixed depression and
dementia"/ or *organic depression/ or *reactive depression/ or *recurrent brief depression/
39. or/2-6
40. 38 or 39
41. exp *side effect/
42. (harm? or adverse or side effect?).tw.
43. 40 and 42
44. 41 or 42
45. 40 and 44
46. exp *antidepressant agent/ae, to [Adverse Drug Reaction, Drug Toxicity]
47. 45 or 46
48. 5 hydroxytryptophan/
49. exp vitamin/
50. exp Fatty Acids, Omega-3/
51. exp acupuncture/
52. exp exercise/
53. massage/
54. Relaxation Therapy/
55. phototherapy/
56. light therapy.tw.
57. Hypericum perforatum/
58. methylfolate.tw.
59. folic acid/
60. S-Adenosylmethionine/
61. SAM-e.tw.
62. (cbt or cognitive behavio?r therapy).tw.
63. cognitive behavior therapy/
64. inositol/
65. saffron/
66. crocus/
67. tryptophan/
68. exp diet therapy/
69. or/48-68
70. 40 and 69
71. (adjunct* or augment*).tw.
72. 40 and 71
73. 37 or 47 or 70 or 72
74. (editorial or note).pt.
75. 73 not 74
76. limit 75 to human
77. review.pt,sh.
78. 76 and 77
79. meta analysis/
80. meta-analysis.ti,ab.
81. (meta anal$ or metaanal$).ti,ab.
82. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
83. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
84. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
85. (medline or embase or cochrane).ti,ab.
86. or/83-85
87. review.pt,sh.
88. 86 and 87
89. or/79-82
90. 89 or 88
91. 76 and 90
92. 78 not 91
93. 76 not 92
94. limit 93 to yr=1980-current
95. limit 94 to english language

Ovid-PsycINFO
April 13 2011
1. major depression/ or dysthymic disorder/ or endogenous depression/ or reactive depression/ or recurrent depression/ or atypical depression/ or "depression (emotion)"/
2. dysthm*.tw.
3. (subclinical adj2 depressi*).tw.
4. (subsyndromal adj2 depressi*).tw.
5. (subthreshold adj2 depressi*).tw.
6. (subdiagnostic adj2 depressi*).tw.
7. or/1-6
8. ((difficult or hard) adj3 treat).tw.
9. augmentation.tw.
10. nonrespon*.tw.
11. non-respon*.tw.
12. switch*.tw.
13. ((insufficient or inadequate or incomplete) adj3 response).tw.
14. (srsi? adj3 (resist* or fail* or response or refractory)).tw.
16. ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
17. ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
18. or/8-17
19. 18 and 7
20. treatment resistant depression/
21. ((treatment resistant or refractory) adj3 depressi*).tw.
22. or/19-21
23. cognitive behavior therapy/ or cognitive therapy/
24. phototherapy/
25. "hydroxytryptophan (5-)"/
26. light therapy.tw.
27. exp exercise/
28. acupuncture/
29. massage/
30. exp relaxation therapy/
31. exp vitamins/ or vitamin therapy/
32. hypericum perforatum/
33. (S-Adenosylmethionine or SAM-e).tw.
34. folic acid/
35. fatty acids/
36. saffron.tw.
37. inositol.tw.
38. exp tryptophan/
39. or/23-38
40. serotonin reuptake inhibitors/ or citalopram/ or fluoxetine/ or fluvoxamine/ or paroxetine/
41. sertraline/
42. (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or seropram).mp.
43. (escitalopram or es citalopram or lexapro or cipralex or esertia).mp.
44. (fluvoxamine or luvox or fèvarin or faverin or dumyrox or favoxil or movox).mp.
45. (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or lovan).mp.
46. (paroxetine or paxil or seroxat or sereupin or aropax or deroxat or rexin or xetanor or paroxat).mp.
47. (sertraline or zoloft or lustral or serlain).mp.
48. ssri?.mp.
49. selective serotonin reuptake inhibit*.mp.
50. symbyax.mp.
51. or/40-50
52. *major depression/ or *dysthymic disorder/ or *endogenous depression/ or *reactive depression/ or *recurrent depression/ or *treatment resistant depression/ or *"depression (emotion)"
53. or/2-6
54. 52 or 53
55. (harm? or adverse or "side effect?").tw.
56. adverse effects.id.
57. exp "side effects (treatment)"
58. drug interactions/
59. exp toxicity/
60. (adjunct* or augment*).tw.
61. or/55-60
62. 39 or 61
63. 54 and 62
64. 7 and 51
65. 22 or 63 or 64
66. limit 65 to human
67. limit 66 to ("comment/reply" or editorial or encyclopedia entry or obituary or review-book or
review-media or review-software & other)
68. 66 not 67
69. limit 68 to yr="1980 -Current"
70. limit 69 to english language

OVID-Cochrane Central Register of Controlled Trials
April 13 2011
1. dysthm*.tw.
2. (subclinical adj2 depressi*).tw.
3. (subsyndromal adj2 depressi*).tw.
4. (subthreshold adj2 depressi*).tw.
5. (subdiagnostic adj2 depressi*).tw.
6. Depression/
7. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
8. or/1-7
9. serotonin uptake inhibitors/ or citalopram/ or fluoxetine/ or fluvoxamine/ or paroxetine/ or sertraline/
10. (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or seropram).mp.
11. (escitalopram or es citalopram or lexapro or cipralex or esertia).mp.
12. (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or lovan).mp.
13. (fluvoxamine or luvox or fevarin or faverin or dumyrox or favoxil or movox).mp.
14. (paroxetine or paxil or seroxat or sereupin or aropax or deroxat or rexetin or xetanor or paroxat).mp.
15. (sertraline or zoloft or lustral or serlain).mp.
16. ssri?.mp.
17. selective serotonin reuptake inhibit*.tw.
18. symbyax.mp.
19. or/9-18
20. Drug Resistance/
21. treatment failure/
22. Retreatment/
23. ((difficult or hard) adj3 treat).tw.
24. augment*.tw.
25. nonrespon*.tw.
26. non-respon*.tw.
27. switch*.tw.
28. ((insufficient or inadequate or incomplete) adj3 respon*).tw.
29. (ssri? adj3 (resist* or fail* or respon* or refractory)).tw.
30. (partial adj3 respon*).tw.
31. ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
32. ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
33. ((treatment resistant or refractory) adj3 depressi*).tw.
34. or/20-32
35. 8 and 34
36. 35 or 33
37. 8 and 19
38. 36 or 37
39. *depression/ or *depressive disorder/ or *depressive disorder, major/ or *dysthymic disorder/
40. or/1-5
41. 39 or 40
42. 5-Hydroxytryptophan/
43. phototherapy/
44. light therapy.tw.
45. exp Exercise/ae, th [Adverse Effects, Therapy]
46. exp Exercise Therapy/
47. exp Acupuncture Therapy/
48. exp Massage/
49. Relaxation Therapy/
50. exp vitamins/
51. Hypericum/
52. john* wort.tw.
53. deplin.tw.
54. methylfolate.tw.
55. Folic Acid/
56. S-Adenosylmethionine/
57. "SAM-e".tw.
58. exp Fatty Acids, Omega-3/
59. Cognitive Therapy/
60. Crocus/
61. Tryptophan/
62. exp Inositol/
63. or/42-62
64. 41 and 63
65. (harm? or adverse or "side effect?").tw.
66. (adjunct* or augment*).tw.
67. 65 or 66
68. 41 and 67
69. exp *antidepressive agents/ae, to [Adverse Drug Reaction, Drug Toxicity]
70. 68 or 69
71. 38 or 64 or 70
72. limit 71 to yr="1980-Current"

OVID-AMED
1. depression/
2. dysthm*.tw.
3. (subclinical adj2 depressi*).tw.
4. (subsyndromal adj2 depressi*).tw.
5. (subthreshold adj2 depressi*).tw.
6. (subdiagnostic adj2 depressi*).tw.
7. or/1-6
8. antidepressive agents/
9. (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or seropram).mp.
10. (escitalopram or es citalopram or lexapro or cipralex or esertia).mp.
11. (fluvoxamine or luvox or fevarin or faverin or dumyrox or favoxil or movox).mp.
12. (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or lovan).mp.
13. (paroxetine or paxil or seroxat or sereupin or aropax or deroxat or rexetin or xetanor or paroxat).mp.
14. (sertraline or zoloft or lustral or serlain).mp.
15. ssri?.mp.
16. selective serotonin reuptake inhibit*.tw.
17. or/8-16
18. 7 and 17
19. ((difficult or hard) adj3 treat).tw.
20. (adjunct* or augment*).tw.
21. nonrespon*.tw.
22. non-respon*.tw.
23. switch*.tw.
24. ((insufficient or inadequate or incomplete) adj3 response).tw.
25. (ssri? adj3 (resist* or fail* or response or refractory)).tw.
27. ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
28. ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
29. or/19-28
30. 7 and 29
31. ((treatment resistant or refractory) adj3 depressi*).tw.
32. 30 or 31
33. cognitive behavior therapy/ or cognitive therapy/
34. phototherapy/
35. hydroxytryptophan.tw.
36. light therapy.tw.
37. exp exercise therapy/
38. exp acupuncture therapy/
39. massage/
40. exp relaxation/
41. exp vitamins/
42. hypericum perforatum/
43. (S-Adenosylmethionine or SAM-e).tw.
44. exp complementary therapies/
45. folic acid/
46. exp fatty acids/
47. crocus/
48. saffron.tw.
49. inositol.tw.
50. tryptophan/
51. or/33-50
52. 7 and 51
53. (harm? or adverse or "side effect?").tw.
54. adverse effects/
55. or/53-54
56. 7 and 55
57. 18 or 32 or 52 or 56
58. limit 57 to (commentary or editorial or interview or news or notes)
59. 57 not 58
60. limit 59 to english
61. limit 60 to yr="1980 -Current"

**EBSCO-CINAHL**

S2  TX Hydroxytryptophan
S3  (MH "Therapeutic Exercise+")
S4  (MH "Alternative Therapies+")
S5  (MH "Massage+")
S7  (MH "Simple Relaxation Therapy (Iowa NIC)")
S8  (MH "St. John's Wort")
S9  "methylfolate"
S10  (MH "Folic Acid+")
S11  (MH "S-Adenosylmethionine")
S12  TX SAM-e
S13  (MH "Fatty Acids, Omega 3+")
S14  (MH "Cognitive Therapy")
S15  "saffron"
S16  (MH "Tryptophan")
S17  (MH "Inositol")
S18  S2 or S3 or S4 or S5 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S19  (MM "Depression")
S20  (MM "Depression, Reactive")
S21  (MM "Dysthymic Disorder")
S22  S19 or S20 or S21
S23  (S19 or S20 or S21) and (S18 and S22)
S24  Limiters - Publication Year from: 1980-2009
S25  S23 and S24
S26  Limiters - Publication Type: Accreditation, Advice and Referral Website, Anecdote, Audiovisual, Bibliography, Biography, Book, Book Chapter, Book Review, Cartoon, Code of
Grey Literature Search

The following sources were search using sensitive searches similar to the searches in bibliographic databases

**Regulatory Information**
- FDA
- Health Canada
- Authorized Medicines for EU

**Clinical Trial Registries**
- ClinicalTrials.gov
- Current Controlled Trials
- Clinical Study Results
- WHO Clinical Trials

**Abstracts and Conference Papers**
- Conference Papers Index
- Scopus

**Grants and Federally Funded Research**
- NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions)
- HSRPROJ (a database providing access to ongoing grants and contracts in health services research)

**Other Miscellaneous Sources**
- Hayes, Inc. Health Technology Assessment
- NY Academy of Medicine’s Grey Literature Index

In addition, the following websites were searched specifically for guidelines on depression treatment

- [http://www.sign.ac.uk/](http://www.sign.ac.uk/)
Appendix B. Forms

Title and Abstract Level I

1. Is this report in English?
○ No (stop)

2. Is this article a commentary/note, letter, editorial, case study, or narrative review (non-systematic review)?
○ Yes (stop)
○ No/can't tell

Instruction for Q2: If the citation is a commentary/note/letter, editorial or is a non-systematic review* (i.e. a review that is not systematic) you should answer "YES" and then go on to the next citation (don't forget to click "submit" or your answers won't be recorded). If the citation is for a PRIMARY study, a clinical practice guideline or a systematic review* (or any study type not listed above) you should answer "NO" and then continue screening. *Look carefully for words like “systematic review”, “meta analysis”, “Cochrane review” or “pooling”, or some description of the methods used to assemble papers: Systematic reviews generally provide a detailed description of their methods that include searches that included more than 1 database (for example, MEDLINE, Embase, PsycINFO, etc.) and specify inclusion and exclusion criteria for eligible studies. - discusses inclusion and exclusion criteria.
- Do not exclude any guideline/recommendation on question2. We will include guidelines/recommendations where they are appropriate.

3. Does this article include subjects who are 12 years of age or older?
○ Yes/can't tell)
○ No (stop)

4. Does this article focus on the “treatment” of depression?
○ Yes/can't tell)
○ No (stop)

5. Does this article have a "primary focus" on "subjects" who have depression (including Dysthmia & Subsyndromal)?
Please answer “no” if the type of depression focused on is:
1. post-partum/puerperal Depression, 2. bipolar depression, 3. seasonal affective disorder 4. post-operative depression 5. premenstrual dysphoric disorder 6. depressive psychosis 7. dysphoria, mourning syndrome 8. pseudodementia
○ Yes/can’t tell
○ No (exclude)

6. Was this report published before 1980?
○ Yes

7. Was this guideline published before 2004?
○ Yes
○ NO
8. **This is a STAR*D publication:**
   - Yes-include
   - Yes-exclude at level 3: ______________
   - Yes- Honorable paper
Title & Abstract Level 2

1. What type of study is this citation?
   ○ Primary study / Can't tell
   ○ Systematic Review / Meta Analysis
   ○ Guideline/ Recommendation (stop)
   ○ None of the above (specify & stop) : ______________________

2. Is the population diagnosed as Major Depressive Disorder (MDD), Dysthymia, or Subsyndromal Depression?
   ○ Yes
   ○ No (stop)
   ○ Can't tell

3. Does the study population include subjects who have failed to respond to treatment previously (if the only treatment they receive is rTMS, or ECT please answer No and go onto Q4)?
   ○ Yes / Can't tell (stop-include)
   ○ No (continue)

Instruction for Q3
We are interested in ANY articles with this group as the population or subpopulation—common terms to identify this population are:
   · Treatment resistant, inadequate response, failed treatment, refractory depression
Sometimes they identify this population by the treatment commonly received after failure—common terms include:
   · Augment/augmentation, switching, optimizing, changing dose,
Also respond “yes” to studies that focus on predictors of response rather than treatment efficacy / effectiveness

4. Does this study focus primarily on the following:
   ○ Efficacy / effectiveness of an SSRI (monotherapy)
   ○ Efficacy / effectiveness of a COMBINED treatment
   ○ Efficacy / effectiveness of a NON-pharmacological treatment (monotherapy)
   ○ Adverse events related to medications
   ○ Other (specify in box intervention or population) : ____________________________
   ○ Efficacy / effectiveness of Non-SSRI drug intervention

This is a relevant guideline for this SR. Extract the data:
   ○ Yes : ______________________________
   ○ No : ______________________________

Investigators comments:
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
Full Text Screening, Level 3

1. **What is the study design described in this study?**
   - RCT (randomized control trial) or CCT (clinical control trial)
   - Cohort / Longitudinal
   - Case-Control
   - Cross-Sectional
   - Interrupted time series with comparator group
   - Systematic Review / Meta analysis (stop)
   - Guideline / Recommendation (stop)
   - Non-comparative design (before-after study, case series, or case report) (stop)
   - Other (specify and can include qualitative studies, editorials, commentaries, etc) (stop)

2. **Is the study population diagnosed primarily (>50%) with Dementia (Alzheimer's Disease, Vascular dementia, etc), Stroke (cerebrovascular accident), Parkinson's disease, Hypothyroidism, or Cushing's Syndrome?**
   - Yes (stop)
   - No / Can't tell (continue)

3. **Were the study subjects (diagnosed with MDD, Dysthymia, or Subsyndromal depression) recruited because they had failed to respond to an SSRI?**
   - YES – ALL (100%) of the subjects demonstrated an inadequate response to an SSRI as a part of this study
   - YES - ALL (100%) of the subjects, based on history, had an inadequate response to an SSRI prior to the start of the current study
   - YES - Some of the subjects had an inadequate response to an SSRI determined by history, and some by demonstration in this study
   - NO - All (100%) of the subjects had an inadequate response to a NON-SSRI anti-depressant determined by history, or by demonstration in this study (STOP)
   - NO - All (100%) of the subjects had an inadequate response to a SSRI combination therapy determined by history, or by demonstration in this study (STOP)
   - NO - All (100%) of the subjects had an inadequate response to a NON-SSRI combination therapy determined by history, or by demonstration in this study (STOP)
   - NO - All (100%) of the subjects had NOT failed to respond in this study (STOP)
   - Can’t tell if the subjects failed to respond to an SSRI or any other anti-depressant (STOP)

Q3: INSTRUCTION

**Demonstrated an inadequate response to SSRI as a part of this study** means that at the start/enrolment of the study patients are given/started on an SSRI and then followed forward in time to determine who did and did not respond adequately. Those subjects who did NOT respond adequately continued on in the study and were then managed with

1) a NEW intervention / treatment OR
2) Switched to a different dose OR
3) Changed to a different duration of the SSRI OR
4) Combined the SSRI with another medication or supplement

**Based on history had an inadequate response to SSRI prior to this study means:**

1) that the subjects enter the study currently taking an SSRI and the investigators assess that their response is not adequate
2) subjects report their past history and indicate that they were on an SSRI previously and they did not have an adequate response, but they are currently not on the medication. The investigators must determine their past inadequate response from patient self-report or medical records.
4. Does the study include any of the following monotherapy interventions in the patients? (check all that apply)
   - Change the dose or duration of the same SSRI
   - Change/switch to another SSRI
   - Change/switch to an antidepressant medication of another class
   - Change to a non-pharmacological intervention (only included list of interventions)
   - NONE of the above (continue)

5. Does the study include any of the following combined therapy interventions in the patients? (check all that apply)
   - Adjunct therapy: addition of an augmenter (i.e. a drug that has no formal indication as monotherapy treatment for unipolar depression, or as a food supplement)
   - Adjunct therapy: addition of a second SSRI or antidepressant from another class
   - Adjunct therapy: addition of a non-pharmacological therapy (see list)
   - Combinations of any of the interventions listed above or other interventions
   - NONE of the above (continue)

6. Does this study focus on the outcomes (primary, secondary, and harm) of interest for our review?
   - Yes
   - No
   - Other (specify): ____________________________

Q6: INSTRUCTION
Other outcomes could include measures of cardiovascular disease, or other biological markers.
Primary Outcomes: Partial or complete response, Remission (free of all symptoms or with few symptoms), Speed of response or remission, and Relapse
Secondary Outcomes: Quality of life, Adherence, Return to work, Global change, External service utilization
Harms: Treatment emergent symptoms as follows: Sexual dysfunction symptoms, Neuropsychiatric symptoms or sedation, Gastrointestinal disturbances, Weight gain or metabolic disturbance, Sleep, Cardiovascular system problems, Geriatric toxicity problems, Other common adverse effects (for example, headaches, orthostatic hypotension, hypertension)

7. Investigators comments:
   _________________________________________________________________________________________________
   _________________________________________________________________________________________________
   _________________________________________________________________________________________________
   _________________________________________________________________________________________________

8. STARD/TORDIA
   - Yes (exclude): ______________________________
   - Yes (include): ______________________________

9. If this study is a STARD/TORDIA study, is this one of the following (all excludes).
   - An overview: ______________________________
   - A study with only phase 1 data: ______________________________
   - Other: ______________________________

10. This is a guideline/recommendation before 2004:
    - Yes
11. **This is a guideline/recommendation that should be excluded because of:**
   ○ Focus on diagnosis or screening rather than treatment
   ○ Not a population of interest
   ○ Not a guideline
   ○ Companion: ______________________________
   ○ Other: ______________________________

12. **The following options are the result of contact with author(s) on "Some" list OR a citation that did not have full text after 2 failed attempts to contact the author(s):**
   ○ Responded and can't provide data
   ○ Did not respond
   ○ Unable to contact (wrong email address; can't find them)
   ○ Responded but beyond our cut date
   ○ Responded and provided data
   ○ Need another FU
   ○ Other: ______________________________
   ○ Exclude: ______________________________

13. **Note from the result of contact with author(s) on "Some" list:**
    __________________________________________________________________________________________
    __________________________________________________________________________________________
1. **Level 4 Data Extraction - Primary Studies (General Information)(Groupin)**
   - Group1: ______________________________
   - Group2: ______________________________
   - Group3: ______________________________
   - Exclude

2. **STUDY**
   - Companion paper: ______________________________
   - Honorable mention: ______________________________
   - Data included/extracted

3. **Country(s) in which study was conducted:**
_____________________________________________________________________________________________

4. **Funding source** (mark NR if not reported)
_____________________________________________________________________________________________

**METHODOLOGY**

5. **Study type (If it is a multicentral study, please provide the number of centers in the box)**
   - □ RCT: ______________________________
   - □ Non-RCT: ______________________________
   - □ Cohort/longitudinal: ______________________________
   - □ Case-Control: ______________________________
   - □ Cross-Sectional: ______________________________
   - □ Other (specify): ______________________________

6. **Setting**
   - □ Outpatient Psychiatric
   - □ Inpatient Psychiatric
   - □ Outpatient Primary Care
   - □ Inpatient Primary Care
   - □ Other (specify): ______________________________

**Table No 1: Type of Intervention/treatment (List all that apply) (specify for each arm/group)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
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</tbody>
</table>

**Table No 2: Sample characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Recruited</td>
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<td>Total Eligible</td>
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<tr>
<td>Total Run-in Phase</td>
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<tr>
<td>Sample of non-responders</td>
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<td>RANDOMIZED or GROUPED</td>
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<tr>
<td>For each time point that has results provided (labeled as T1, T2, T3)</td>
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<tr>
<td>Total who withdrew or were lost to follow-up when study outcomes are measured</td>
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<tr>
<td>Withdrawal because of Adverse Effects</td>
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<tr>
<td>Withdrawal because of Loss to Follow-up</td>
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<tr>
<td>Total number of subjects analyzed</td>
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</table>

**POPULATION CHARACTERISTICS**

**Table No 3: Age**

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
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<td>Max</td>
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<td>Median</td>
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<td>IQR</td>
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<tr>
<td>Other (e.g. age group)</td>
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</tbody>
</table>

**Table No 4: Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (No)</td>
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<td></td>
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<tr>
<td>Male (%)</td>
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<tr>
<td>Female (No)</td>
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<tr>
<td>Female (%)</td>
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</tbody>
</table>
Table No 5: Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
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</thead>
<tbody>
<tr>
<td>White (No)</td>
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<td>Hispanic (No)</td>
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<tr>
<td>African-American (No)</td>
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<td>Oriental (No)</td>
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<tr>
<td>Asian (No)</td>
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<tr>
<td>Other (specify) (No)</td>
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231. List all Inclusion criteria
☐ 1: ______________________________
☐ 2: ______________________________
☐ 3: ______________________________
☐ 4: ______________________________
☐ 5: ______________________________
☐ 6: ______________________________
☐ 7: ______________________________
☐ 8: ______________________________

232. List all Exclusion criteria
☐ 1: ______________________________
☐ 2: ______________________________
☐ 3: ______________________________
☐ 4: ______________________________
☐ 5: ______________________________
☐ 6: ______________________________
☐ 7: ______________________________
☐ 8: ______________________________

DISEASE

233. Diagnosis (list all that apply)
☐ Major Depressive Disorder (MDD)
☐ Dysthymia
☐ Subsyndromal
☐ Other (specify): ______________________________

234. Method(s) used to diagnose Depression:
☐ 1: ______________________________
☐ 2: ______________________________
☐ 3: ______________________________
☐ 4: ______________________________
☐ 5: ______________________________
☐ 6: ______________________________
☐ 7: ______________________________
☐ 8: ______________________________
235. **Method of determining inadequate response** (click all that apply and provide as much detail as possible. e.g. proportion).

- □ Prospective (Screening or Run-in Phase) : ______________________________
- □ Retrospective: Medical chart : ______________________________
- □ Retrospective: Patient self report of history of failure : ______________________________
- □ Retrospective: Patient self report of history of adverse event response : ______________________________
- □ Retrospective: Currently on medication to which they have not responded : ______________________________
- □ Retrospective: Confirmation by clinician : ______________________________
- □ Other (specify) : ______________________________

236. **Who determined previous treatment failure?**

_____________________________________________________________________________________________

### Table No 6: Length of current Episode

<table>
<thead>
<tr>
<th>Length</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
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<tbody>
<tr>
<td>Min</td>
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</tbody>
</table>

301. **Specify units in the mean for table 6 (above table).**

- □ Week : ______________________________
- □ Day : ______________________________
- □ Month : ______________________________
- □ Year : ______________________________

### Table No 7: Past Mental Health History (episodes of Depression over lifetime)

<table>
<thead>
<tr>
<th>No of past episode</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
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<td>Max</td>
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<td>SD</td>
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</tr>
</tbody>
</table>
Table No 8: Type and number of SSRI(s) that had previously failed to respond to (List all that apply) (specify for each arm/group)

<table>
<thead>
<tr>
<th>Type/No</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
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</thead>
<tbody>
<tr>
<td>Type</td>
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<tr>
<td>No of drugs</td>
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</tbody>
</table>

**INTERVENTION**

390. Were patients tapered off existing medications prior to start of the study?
   ○ Yes: ______________________________
   ○ No: ______________________________
   ○ Unclear: ______________________________

391. Was a run-in phase employed?
   □ Yes (specify time in weeks): ______________________________
   □ No: ______________________________

392. Was there a washout period following the run-in phase? (If yes, specify the time-interval)
   ○ Yes: ______________________________
   ○ No: ______________________________
   ○ Unclear: ______________________________

393. PURPOSE OF TREATMENT

________________________________________

394. What type of patients are excluded from proceeding to the next phase of treatment (List all criteria)?
   □ 1: ______________________________
   □ 2: ______________________________
   □ 3: ______________________________
   □ 4: ______________________________
   □ 5: ______________________________
   □ 6: ______________________________
   □ 7: ______________________________
   □ 8: ______________________________
**Table No 9: Dose of treatment/intervention**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (minimum)</td>
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<td></td>
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<tr>
<td>Initial (maximum)</td>
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<tr>
<td>Final (minimum)</td>
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<tr>
<td>Final (maximum)</td>
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<td>Other</td>
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</tbody>
</table>

**Table No 10: Treatment interval (week) of treatment/intervention for arm1/group1**

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
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<td></td>
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<td>Max</td>
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<tr>
<td>Mean</td>
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<td>SD</td>
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<tr>
<td>SEM</td>
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<td></td>
</tr>
<tr>
<td>Median</td>
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<td></td>
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<tr>
<td>IQR</td>
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<tr>
<td>Other</td>
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</tbody>
</table>

499. **Specify units in the mean for table 10 (above table).**

- Week: ______________________________
- Day: ______________________________
- Month: ______________________________
- Year: ______________________________

500. **Type of treatment provider (describe in brief):**

- Psychiatrist: ______________________________
- Family Physician: ______________________________
- Allied Health: ______________________________
- Other: ______________________________
RESULTS

Table No 11: Time points at which treatment discontinued (specify when outcomes were collected and the length of follow up in week(s))

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Week(s)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate</td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td></td>
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<tr>
<td>Follow Up</td>
<td></td>
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</tr>
</tbody>
</table>

511. Patient Compliance (Detail definition if provided) (list all methods):

☐ 1: ______________________________
☐ 2: ______________________________
☐ 3: ______________________________
☐ 4: ______________________________
☐ 5: ______________________________
☐ 6: ______________________________
☐ 7: ______________________________
☐ 8: ______________________________

Table No 12: Compliance with treatment (End Point) (indicate compliance or non-compliance in the last box)

<table>
<thead>
<tr>
<th>Comply</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
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<td>Max</td>
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<td>Mean</td>
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<tr>
<td>Median</td>
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<tr>
<td>IQR</td>
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</tr>
</tbody>
</table>
584. **Percent (%) or number of subjects declaring use of Complementary and Alternative Medicine (CAM) interventions**

- [ ] Baseline (No): ______________________________
- [ ] Baseline (%): ______________________________
- [ ] Concurrent (No): ______________________________
- [ ] Concurrent (%): ______________________________

585. **Are there stratified ANALYSES for the following variables/factors (check all that apply):**

- [ ] Depressive diagnosis (MDD vs Other): ______________________________
- [ ] Disease severity: ______________________________
- [ ] Age: ______________________________
- [ ] Gender: ______________________________
- [ ] Race: ______________________________
- [ ] Socioeconomic status: ______________________________
- [ ] Medical comorbidities: ______________________________
- [ ] Psychiatric comorbidities: ______________________________
- [ ] other: ______________________________
- [ ] other: ______________________________
- [ ] other: ______________________________

586. **List all relevant outcomes/instruments used in this study. Place a (P) after the outcomes indicating that they are the primary outcomes.**

- [ ] 1: ______________________________
- [ ] 2: ______________________________
- [ ] 3: ______________________________
- [ ] 4: ______________________________
- [ ] 5: ______________________________
- [ ] 6: ______________________________
- [ ] 7: ______________________________
- [ ] 8: ______________________________

587. **Overall conclusions on efficacy from an abstract if no/short results reported:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________

588. **Additional comments or important notes about this study:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________

589. **Go to Data Extraction form for Harm**

- [ ] Yes
- [ ] No
590. **Investigator 1 Comments:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

591. **Investigator 2 Comments:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

592. **Investigator 3 Comments:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

593. **Group**

☐ MoCo : ______________________________
☐ MoMo : ______________________________
☐ CoCo : ______________________________
☐ STARD : ______________________________
☐ Other : ______________________________
1. **Data Extraction, Primary Study-Harm (Grouping)**
   - Group1: ______________________________
   - Group2: ______________________________
   - Group3: ______________________________
   - Exclude

2. **Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

3. **Were the harms PRE-DEFINED using standardized or precise definitions?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

4. **Were SEVERE events precisely defined?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

5. **Were SERIOUS events precisely defined?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

6. **Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

7. **Was the mode of harms collection specified as:**
   - Active: ______________________________
   - Passive: ______________________________
   - Not Reported: ______________________________
   - Unclear: ______________________________

8. **Did the study specify WHO collected the harms?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________

9. **Did the study specify the TRAINING or BACKGROUND of who ascertained the harms (specify)?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: ______________________________
10. **Did the study specify the TIMING and FREQUENCY of collection of the harms (specify)?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: __________________________

11. **Did the author(s) specify the type of analyses undertaken for harms data (specify)?**
   - Yes: ______________________________
   - No: ______________________________
   - Unclear: __________________________

**Table No 1: Type of Intervention/treatment, sample size, Adverse Events (AE), and Withdrawals per group**

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Pts assigned</td>
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<tr>
<td>No of Pts who have AE</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Percent of Pts who have AE</td>
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<tr>
<td>No of Pts who withdrew due to AE</td>
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<tr>
<td>Percent of Pts who withdrew</td>
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</tbody>
</table>

**Table No 2: Identify number (%) of patients who had severe or serious adverse events (AE) per group**

<table>
<thead>
<tr>
<th>Severe AD</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
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</thead>
<tbody>
<tr>
<td>Suicidality</td>
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<td>Death</td>
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<tr>
<td>Other 1</td>
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<td>Other 2</td>
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<td>Other 3</td>
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<td>Other 4</td>
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</tbody>
</table>
Table No 3: Identify number (%) of patients who had adverse events (AE) per group

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Dysfunction</td>
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<td>Anxiety</td>
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<td>Sedation</td>
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<tr>
<td>Gastrointestinal Disturbance (nausea, vomiting, diarrhea)</td>
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<tr>
<td>Weight Loss</td>
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<td>Weight Gain</td>
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<tr>
<td>Change in triglycerides</td>
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<tr>
<td>Change in glucose</td>
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<tr>
<td>Sleep disorder (insomnia or hypersomnia)</td>
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<tr>
<td>Cardiovascular Problems (hypotension, tachycardia, bradycardia)</td>
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<td>Toxicity problems</td>
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<td>Other 1</td>
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<td></td>
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<td>Other 2</td>
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<td></td>
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<td>Other 3</td>
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<td>Other 4</td>
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<td>Other 5</td>
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</tr>
</tbody>
</table>

278. **Data Extractor/Reviewer:**

_____________________________________________________________________________________________

279. **Comments:**

_____________________________________________________________________________________________

_____________________________________________________________________________________________
280. **First Reviewer:**

281. **First Reviewer comments:**

282. **Second Reviewer:**

283. **Second Reviewer Comments:**

284. **Investigators Comments:**

285. **Go to outcome form**

☐ Yes

☐ NO

286. **New Question**

287. **Group**

☐ MoCo

☐ MoMo

☐ CoCo

☐ STARD

☐ Other: ______________________________
1. **Quality Assessment for Primary Studies Rater #1 (Grouping)**
   ○ Group1: ______________________________
   ○ Group2: ______________________________
   ○ Group3: ______________________________
   ○ Exclude

**Instruction:** Please read the instructions that were sent to you by email before completing this form.

2. **Was the method of randomization adequate?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

3. **Was the treatment allocation concealed?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

   *Was knowledge of the allocated interventions adequately prevented during the study?*

4. **Was the patient blinded to the intervention?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

5. **Was the care provider blinded to the intervention?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

6. **Was the outcome assessor blinded to the intervention?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

   *Were incomplete outcome data adequately addressed?*

7. **Was the drop-out rate described and acceptable?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

8. **Were all randomized participants analyzed in the group to which they were allocated?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

9. **Are reports of the study free of suggestion of selective outcome reporting?**
   ○ Yes  ○ No  ○ Unsure: ______________________________

**Other sources of potential bias:**

10. **Were the groups similar at baseline regarding the most important prognostic indicators?**
    ○ Yes  ○ No  ○ Unsure: ______________________________

11. **Were co-interventions avoided or similar?**
    ○ Yes  ○ No  ○ Unsure: ______________________________

12. **Was the compliance acceptable in all groups?**
    ○ Yes  ○ No  ○ Unsure: ______________________________

13. **Was the timing of the outcome assessment similar in all groups?**
    ○ Yes  ○ No  ○ Unsure: ______________________________
14. **Is the role of the study sponsor/funder (i.e. manufacturer of the device) appropriate?**
   ○ Yes  ○ No  ○ Unsure : ______________________________

15. **Go to level 5**
   ○ Yes

16. **Other:**

   __________________________________________________________________________________________
   __________________________________________________________________________________________
1. **Quality Assessment for Primary Studies Rater #2 (Grouping)**
   - Group1: ______________________________
   - Group2: ______________________________
   - Group3: ______________________________
   - Exclude: ______________________________

**Instruction:** Please read the instructions that were sent to you by email before completing this form.

2. **Was the method of randomization adequate?**
   - Yes  ○ No  ○ Unsure : ______________________________

3. **Was the treatment allocation concealed?**
   - Yes  ○ No  ○ Unsure : ______________________________

**Was knowledge of the allocated interventions adequately prevented during the study?**

4. **Was the patient blinded to the intervention?**
   - Yes  ○ No  ○ Unsure : ______________________________

5. **Was the care provider blinded to the intervention?**
   - Yes  ○ No  ○ Unsure : ______________________________

6. **Was the outcome assessor blinded to the intervention?**
   - Yes  ○ No  ○ Unsure : ______________________________

**Were incomplete outcome data adequately addressed?**

7. **Was the drop-out rate described and acceptable?**
   - Yes  ○ No  ○ Unsure : ______________________________

8. **Were all randomized participants analyzed in the group to which they were allocated?**
   - Yes  ○ No  ○ Unsure : ______________________________

9. **Are reports of the study free of suggestion of selective outcome reporting?**
   - Yes  ○ No  ○ Unsure : ______________________________

**Other sources of potential bias:**

10. **Were the groups similar at baseline regarding the most important prognostic indicators?**
    - Yes  ○ No  ○ Unsure : ______________________________

11. **Were co-interventions avoided or similar?**
    - Yes  ○ No  ○ Unsure : ______________________________

12. **Was the compliance acceptable in all groups?**
    - Yes  ○ No  ○ Unsure : ______________________________

13. **Was the timing of the outcome assessment similar in all groups?**
    - Yes  ○ No  ○ Unsure : ______________________________
14. **Is the role of the study sponsor/funder (i.e. manufacturer of the device) appropriate?**
   ○ Yes ○ No ○ Unsure : ______________________________

15. **Other:**
   _______________________________________________________________________________________
   _______________________________________________________________________________________

16. **Group**
   □ MoCo
   □ MoMo
   □ CoCo
   □ STARD
   □ Other : ______________________________
**Data Extraction - Primary Study - outcome (Grouping)**

- Group 1: ______________________________
- Group 2: ______________________________
- Group 3: ______________________________
- Exclude

**Table 1: List the time interval (wks) where study outcomes were collected**

<table>
<thead>
<tr>
<th>Study Outcome</th>
<th>Time Intervals (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For prospective studies ONLY, identify the time interval from the start of the prospective evaluation of treatment response (baseline0) to the point of evaluation for non-response.</td>
<td></td>
</tr>
<tr>
<td>For prospective and retrospective studies, identify the time interval from the start of the study with subjects who are non-responders (baseline1) to the following time points:</td>
<td></td>
</tr>
<tr>
<td>Intermediate time point #1.</td>
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<tr>
<td>Intermediate time point #2.</td>
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<tr>
<td>Intermediate time point #3.</td>
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<tr>
<td>End point or final time point</td>
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<tr>
<td>Other #1:</td>
<td></td>
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<tr>
<td>Other #2:</td>
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</tr>
</tbody>
</table>

**Table 1, Remark/Note:**

________________________________________________________________________________________

**Table 2: List all outcomes (Response and/or Remission) and place a Y in the Time cell to indicate when these were collected. Please read helpfile carefully.**

<table>
<thead>
<tr>
<th>List all reported outcomes</th>
<th>Measurement Tool (e.g. HAMD)</th>
<th>Primary (P)</th>
<th>Secondary (S)</th>
<th>Time 0 (Baseline)</th>
<th>Time 1 (Intermediate)</th>
<th>Time 2 (Intermediate)</th>
<th>Time 3 (Intermediate)</th>
<th>Time Final (End point)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>Primary (P)</td>
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</table>
Table 2: Remark/Note:

Table 3: List Study definitions of the following:

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<thead>
<tr>
<th>Outcome</th>
<th>Measurement Tool (e.g. HAMD)</th>
<th>Score threshold (e.g. &gt;12)</th>
<th>Definitions</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate Response (responders)</td>
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<tr>
<td>Inadequate Response (non-responders)</td>
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<td>Partial Response (partial responders)</td>
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<td>Remission (remitters)</td>
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<tr>
<td>Non-remission</td>
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</tbody>
</table>

Table 4: Endpoint Dichotomous Outcome 1 with Measurement Tool 1

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<th>Outcome 1/ Tool 1</th>
<th>Entire Population</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
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Table 4—Remark/Note:
_____________________________________________________________________________________________
_____________________________________________________________________________________________

Table 5: Endpoint Dichotomous Outcome 1 with Measurement Tool 2

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<th>Group 7</th>
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### Table 5–Remark/Note:

_____________________________________________________________________________________________

_____________________________________________________________________________________________

Table 6 : Endpoint Dichotomous Outcome 2 with Measurement Tool 1

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<th>Group 4</th>
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<th>Group 6</th>
<th>Group 7</th>
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<td>Significant level (e.g. 90%, 95%, 99%)</td>
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</table>

Table 7–Remark/Note:
_____________________________________________________________________________________________
_____________________________________________________________________________________________
Specify type of outcome measure in table 8:
- Change score: ______________________________
- Mean score: ______________________________
- Adjusted mean score: ______________________________
- Least square mean change: ______________________________

**Table 8: Endpoint Continuous Outcome 1 with Measurement Tool 1**

<table>
<thead>
<tr>
<th>Outcome 1/Tool 1</th>
<th>Entire Population</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
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<tbody>
<tr>
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<td>Groups compared</td>
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<td>Statistical Test</td>
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<tr>
<td>Significant level (e.g. 90%, 95%, 99%)</td>
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</table>

**Table 8—Remark/Note:**
_____________________________________________________________________________________________
_____________________________________________________________________________________________

Specify type of outcome measure in table 9:
- Change score: ______________________________
- Mean score: ______________________________
- Adjusted mean score: ______________________________
- Least square mean change: ______________________________
### Table 9: Endpoint Continuous Outcome 1 with Measurement Tool 2

<table>
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<th>Entire Population</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
<th>Group 6</th>
<th>Group 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement Tool</td>
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**Table 9—Remark/Note:**

_____________________________________________________________________________________________
_____________________________________________________________________________________________
Specify type of outcome measure in table 10:

- Change score: ______________________________
- Mean score: ______________________________
- Adjusted mean score: ______________________________
- Least square mean change: ______________________________

### Table 10: Endpoint Continuous Outcome 2 with Measurement Tool 1

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<th>Group 1</th>
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### Table 10 – Remark/Note:

_____________________________________________________________________________________________
_____________________________________________________________________________________________

Specify type of outcome measure in table 11:

- Change score: ______________________________
- Mean score: ______________________________
- Adjusted mean score: ______________________________
- Least square mean change: ______________________________

### Table 11: Endpoint Continuous Outcome 2 with Measurement Tool 2

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Table 11—Remark/Note:
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Table 12: Baseline Measurement 1

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<tr>
<th>Baseline Measurement 1</th>
<th>Entire Population</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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Table 12–Remark/Note:
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Table 13: Baseline Measurement 2

Screener’s note/remark:
_____________________________________________________________________________________________
_____________________________________________________________________________________________

1192. New Question
_____________________________________________________________________________________________

1193. New Question
_____________________________________________________________________________________________

1194. New Question
_____________________________________________________________________________________________

B-33
Go to Quality Assessment for Primary Studies
○ Yes
○ No

Investigator's Comments:
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

1197. Group
☐ MoCo
☐ MoMo
☐ CoCo
☐ STARD
☐ Other: ______________________________
1. Is publication date of this guideline 2004 and forward?  
   ○ Yes (continue)  
   ○ No (stop)  

2. What organization sponsored this Guideline?  
   ____________________________________________________________________________  

3. In which country is this guideline applied?  
   ____________________________________________________________________________  

4. What is the scope and purpose of this Guideline/Recommendation? (List all that apply)  
   □ Treatment  
   □ Diagnosis  
   □ Prognosis  
   □ Others (specify): ________________________________  

5. Who are the Intended Users (check all that apply)  
   □ Primary Care Physicians (e.g. General practitioners)  
   □ Mental Health Specialist (Psychiatrists)  
   □ Allied Mental Health Professionals (Social Workers, Mental Health Nurses, Occupational Therapists)  
   □ Patients  
   □ Others (specify)  

6. What is the setting for use of this Guideline? (check all that apply)  
   □ Primary Care  
   □ Mental Health Out Patient Setting  
   □ Mental Health Inpatient Setting  
   □ Others (specify): ________________________________  

7. What is the target population on this Guideline? (check all that apply)  
   □ Adult MDD  
   □ Adult Dysthymia  
   □ Adult Subsyndromal  
   □ Adolescent MDD  
   □ Adolescent Dysthymia  
   □ Adolescent Subsyndromal  
   □ None of the above (stop)  

8. Does this guideline have a specific recommendation (course of action) for patients who do not respond to the intervention(s)?  
   ○ Yes  
   ○ No  
   ○ Not sure  

9. What is the definition of AND method of establishing “inadequate/ unsatisfactory” response?  
   ____________________________________________________________________________
Recommendation #1 for populations who failed to respond to previous antidepressants:

10. Specify Recommendation #1 for populations who failed to respond to previous antidepressants. (Please type in the exact wording)

_____________________________________________________________________________________________
_____________________________________________________________________________________________

11. Does the recommendation identify or stratify actions or suggestions based on the specific TYPE of antidepressant medication that subjects had not respond to adequately?
   □ NO: they do NOT specify previous type of antidepressant (go to Q13)
   □ YES: they specify the type of antidepressant

12. Specify the type/class of DRUG intervention (check all that apply)
   □ SSRI (specify) : ______________________________
   □ SNRI (specify) : ______________________________
   □ SSNRI (specify) : ______________________________
   □ Other second generation antidepressants (specify) : ______________________________
   □ None Pharmacological (specify) : ______________________________

13. What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system?)

_____________________________________________________________________________________________

14. Grading of the recommendation #1: (i.e. strong recommendation)

_____________________________________________________________________________________________

15. Rating of quality of evidence for Recommendation #1: (i.e. evidence at high risk of bias, or level I (indicating RCT design)

_____________________________________________________________________________________________

16. For the evidence that is cited to support the recommendation, please list the number and type of studies included: (i.e. 4 RCTs, and 2 Observational studies)

_____________________________________________________________________________________________

17. Does the recommendation ONLY specify actions / suggestions to switch to the use of MONTHERAPY that are generic (not specific to drug or intervention? (Please type in the exact wording)

_____________________________________________________________________________________________

18. Does the recommendation specify any of the following for MONTHERAPY treatment changes? (specify exact wording)
   □ ONLY specify actions / suggestions to switch but is non-specific (Specify exact wording):

   □ Indicates to change the DOSE of the current SSRI or antidepressant : ______________________________
   □ Indicates to change the DURATION of the current SSRI or antidepressant : ______________________________
   □ Indicates a switch from one SSRI to another SSRI OR from one Non-SSRI antidepressant to another within the SAME drug class : ______________________________
   □ Indicates a switch from an SSRI to another non-SSRI anti-depressant of a different class :

   □ Indicates a switch from an SSRI or non-SSRI anti-depressant to a non-pharmacological treatment :
19. **Does the recommendation specify any of the following for COMBINED THERAPY treatment changes: (specify exact wording)**

- □ ONLY specify actions / suggestions to combine therapies but is non-specific : ________________________________

- □ Indicates to combine therapies with Augmenters (drugs or food supplements) : ________________________________

- □ Indicates to combine one SSRI or non-SSRI antidepressant with another SSRI or non-SSRI antidepressant of the SAME class : ________________________________

- □ Indicates to combine one SSRI with another non-SSRI antidepressant : ________________________________

- □ Indicates to combine an SSRI or antidepressant with a non-pharmacological intervention : ________________________________

- □ Indicates to combine an SSRI or antidepressant with multiple combinations (any intervention previously listed) : ________________________________

**Recommendation #2 for populations who failed to respond to previous antidepressants:**

10. **Specify Recommendation #2 for populations who failed to respond to previous antidepressants. (Please type in the exact wording)**

_____________________________________________________________________________________________

_____________________________________________________________________________________________

11. **Does the recommendation identify or stratify actions or suggestions based on the specific TYPE of antidepressant medication that subjects had not respond to adequately?**

- □ NO: they do NOT specify previous type of antidepressant (go to Q13)

- □ YES: they specify the type of antidepressant

12. **Specify the type/class of DRUG intervention (check all that apply)**

- □ SSRI (specify) : ________________________________

- □ SNRI (specify) : ________________________________

- □ SSNRI (specify) : ________________________________

- □ Other second generation antidepressants (specify) : ________________________________

- □ None Pharmological (specify) : ________________________________

13. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system)?**

_____________________________________________________________________________________________

14. **Grading of the recommendation #2: (i.e. strong recommendation)**

_____________________________________________________________________________________________

15. **Rating of quality of evidence for Recommendation #2 : (i.e. evidence at high risk of bias, or level I (indicating RCT design)**

_____________________________________________________________________________________________

16. **For the evidence that is cited to support the recommendation, please list the number and type of studies included: (i.e. 4 RCTs, and 2 Observational studies)**

_____________________________________________________________________________________________

17. **Does the recommendation ONLY specify actions / suggestions to switch to the use of MOTHERAPY that are generic (not specific to drug or intervention? (Please type in the exact wording)**

_____________________________________________________________________________________________
18. **Does the recommendation specify any of the following for MONTHERAPY treatment changes? (specify exact wording)**

- **□** ONLY specify actions / suggestions to switch but is non-specific (Specify exact wording):
  ______________________________
- **□** Indicates to change the DOSE of the current SSRI or antidepressant:
  ______________________________
- **□** Indicates to change the DURATION of the current SSRI or antidepressant:
  ______________________________
- **□** Indicates a switch from one SSRI to another SSRI OR from one Non-SSRI antidepressant to another within the SAME drug class:
  ______________________________
- **□** Indicates a switch from an SSRI to another non-SSRI antidepressant of a different class:
  ______________________________
- **□** Indicates a switch from an SSRI or non-SSRI anti-depressant to a non-pharmacological treatment:
  ______________________________

19. **Does the recommendation specify any of the following for COMBINED THERAPY treatment changes: (specify exact wording)**

- **□** ONLY specify actions / suggestions to combine therapies but is non-specific:
  ______________________________
- **□** Indicates to combine therapies with Augmenters (drugs or food supplements):
  ______________________________
- **□** Indicates to combine one SSRI or non-SSRI antidepressant with another SSRI or non-SSRI antidepressant of the SAME class:
  ______________________________
- **□** Indicates to combine one SSRI with another non-SSRI antidepressant:
  ______________________________
- **□** Indicates to combine an SSRI or antidepressant with a non-pharmacological intervention:
  ______________________________
- **□** Indicates to combine an SSRI or antidepressant with multiple combinations (any intervention previously listed):
  ______________________________

**Recommendation #3 for populations who failed to respond to previous antidepressants:**

10. **Specify Recommendation #3 for populations who failed to respond to previous antidepressants. (Please type in the exact wording)**

_____________________________________________________________________________________________
_____________________________________________________________________________________________

11. **Does the recommendation identify or stratify actions or suggestions based on the specific TYPE of antidepressant medication that subjects had not respond to adequately?**

- **□** NO: they do NOT specify previous type of antidepressant (go to Q13)
- **□** YES: they specify the type of antidepressant

12. **Specify the type/class of DRUG intervention (check all that apply)**

- **□** SSRI (specify):
- **□** SNRI (specify):
- **□** SSNRI (specify):
- **□** Other second generation antidepressants (specify):
- **□** None Pharmacological (specify):

13. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system)?**

_____________________________________________________________________________________________

14. **Grading of the recommendation #3: (i.e. strong recommendation)**

_____________________________________________________________________________________________
15. Rating of quality of evidence for Recommendation #3: (i.e. evidence at high risk of bias, or level I (indicating RCT design)

16. For the evidence that is cited to support the recommendation, please list the number and type of studies included: (i.e. 4 RCTs, and 2 Observational studies)

17. Does the recommendation ONLY specify actions / suggestions to switch to the use of MONTHERAPY that are generic (not specific to drug or intervention? (Please type in the exact wording)

18. Does the recommendation specify any of the following for MONTHERAPY treatment changes? (specify exact wording)
   □ ONLY specify actions / suggestions to switch but is non-specific (Specify exact wording):
   □ Indicates to change the DOSE of the current SSRI or antidepressant: ____________________________
   □ Indicates to change the DURATION of the current SSRI or antidepressant: ____________________________
   □ Indicates a switch from one SSRI to another SSRI OR from one Non-SSRI antidepressant to another within the SAME drug class: ____________________________
   □ Indicates a switch from an SSRI to another non-SSRI antidepressant of a different class:
   □ Indicates a switch from an SSRI or non-SSRI anti-depressant to a non-pharmacological treatment:

19. Does the recommendation specify any of the following for COMBINED THERAPY treatment changes: (specify exact wording)
   □ ONLY specify actions / suggestions to combine therapies but is non-specific:
   □ Indicates to combine therapies with Augmenters (drugs or food supplements):
   □ Indicates to combine one SSRI or non-SSRI antidepressant with another SSRI or non-SSRI antidepressant of the SAME class: ____________________________
   □ Indicates to combine one SSRI with another non-SSRI antidepressant: ____________________________
   □ Indicates to combine an SSRI or antidepressant with a non-pharmacological intervention:
   □ Indicates to combine an SSRI or antidepressant with multiple combinations (any intervention previously listed):

Recommendation #4 for populations who failed to respond to previous antidepressants;

10. Specify Recommendation #4 for populations who failed to respond to previous antidepressants. (Please type in the exact wording)

11. Does the recommendation identify or stratify actions or suggestions based on the specific TYPE of antidepressant medication that subjects had not respond to adequately?
   □ NO: they do NOT specify previous type of antidepressant (go to Q13)
   □ YES: they specify the type of antidepressant
12. **Specify the type/class of DRUG intervention (check all that apply)**
- □ SSRI (specify) : ______________________________
- □ SNRI (specify) : ______________________________
- □ SSNRI (specify) : ______________________________
- □ Other second generation antidepressants (specify) : ______________________________
- □ None Pharmological (specify) : ______________________________

13. **What type of system was used to grade or evaluate the strength of evidence (i.e. GRADE, or some association specific system)?**

14. **Grading of the recommendation #4: (i.e. strong recommendation)**

15. **Rating of quality of evidence for Recommendation #4 : (i.e. evidence at high risk of bias, or level I (indicating RCT design)**

16. **For the evidence that is cited to support the recommendation, please list the number and type of studies included: (i.e. 4 RCTs, and 2 Observational studies)**

17. **Does the recommendation ONLY specify actions / suggestions to switch to the use of MONTHERAPY that are generic (not specific to drug or intervention? (Please type in the exact wording)**

18. **Does the recommendation specify any of the following for MONTHERAPY treatment changes? (specify exact wording)**
- □ ONLY specify actions / suggestions to switch but is non-specific (Specify exact wording) : ______________________________
- □ Indicates to change the DOSE of the current SSRI or antidepressant : ______________________________
- □ Indicates to change the DURATION of the current SSRI or antidepressant : ______________________________
- □ Indicates a switch from one SSRI to another SSRI OR from one Non-SSRI antidepressant to another within the SAME drug class : ______________________________
- □ Indicates a switch from an SSRI to another non-SSRI antidepressant of a different class : ______________________________
- □ Indicates a switch from an SSRI or non-SSRI anti-depressant to a non-pharmacological treatment : ______________________________

19. **Does the recommendation specify any of the following for COMBINED THERAPY treatment changes: (specify exact wording)**
- □ ONLY specify actions / suggestions to combine therapies but is non-specific : ______________________________
- □ Indicates to combine therapies with Augmenters (drugs or food supplements) : ______________________________
- □ Indicates to combine one SSRI or non-SSRI antidepressant with another SSRI or non-SSRI antidepressant of the SAME class : ______________________________
- □ Indicates to combine one SSRI with another non-SSRI antidepressant : ______________________________
- □ Indicates to combine an SSRI or antidepressant with a non-pharmacological intervention : ______________________________
- □ Indicates to combine an SSRI or antidepressant with multiple combinations (any intervention previously listed) : ______________________________
50. Data Extractor/Reviewer:

51. Second Reviewer:

52. This is a companion guideline to:
Level 5: Quality Assessment Tools for Guidelines and Recommendations: AGREE II instrument for Guidelines:

General Instruction, Rating Scale:

All AGREE II items are rated on the following 7-point scale:

Score of 1 (Strongly Disagree). A score of 1 should be given when there is no information that is relevant to the AGREE II item or if the concept is very poorly reported.

Score of 7 (Strongly Agree). A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User’s Manual have been met.

Scores Between 2 and 6. A score between 2 and 6 is assigned when the reporting of the AGREE II item does not meet the full criteria or considerations. A score is assigned depending on the completeness and quality of reporting. Scores increase as more criteria are met and considerations addressed. The “How to Rate” section for each item includes details about assessment criteria and considerations specific to the item. (see instruction)

1. The overall objective(s) of the guideline is (are) specifically described.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

2. The health question(s) covered by the guideline is (are) specifically described.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

4. The guideline development group includes individuals from all the relevant professional groups.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

5. The views and preferences of the target population (patients, public, etc.) have been sought.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

6. The target users of the guideline are clearly defined.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

7. Systematic methods were used to search for evidence.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

8. The criteria for selecting the evidence are clearly described.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

9. The strengths and limitations of the body of evidence are clearly described.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

10. The methods used for formulating the recommendations are clearly described.
    ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
    ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

12. There is an explicit link between the recommendations and the supporting evidence.
    ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7
13. The guideline has been externally reviewed by experts prior to its publication.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

14. A procedure for updating the guideline is provided.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

15. The recommendations are specific and unambiguous.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

16. The different options for management of the condition or health issue are clearly presented.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

17. Key recommendations are easily identifiable.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

18. The guideline describes facilitators and barriers to its application.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

19. The guideline provides advice and / or tools on how the recommendations can be put into practice.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

20. The potential resource implications of applying the recommendations have been considered.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

21. The guideline presents monitoring and / or auditing criteria.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

22. The views of the funding body have not influenced the content of the guideline.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

23. Competing interests of guideline development group members have been recorded and addressed.
○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

24. Overall Assessment:
Would you recommend these guidelines for use in practice?
○ Strongly recommend
○ Recommend (with provisos alteration)
○ Would not recommend
○ Unsure

25. Comments:
26. **Appraiser 1:**
- Catherine
- Sara
- Homa
- Lina
- **Other (specify):** ______________________________
Level 5: Quality Assessment Tools for Guidelines and Recommendations: AGREE II instrument for Guidelines:

General Instruction, Rating Scale:

All AGREE II items are rated on the following 7-point scale:

Score of 1 (Strongly Disagree). A score of 1 should be given when there is no information that is relevant to the AGREE II item or if the concept is very poorly reported.

Score of 7 (Strongly Agree). A score of 7 should be given if the quality of reporting is exceptional and where the full criteria and considerations articulated in the User’s Manual have been met.

Scores Between 2 and 6. A score between 2 and 6 is assigned when the reporting of the AGREE II item does not meet the full criteria or considerations. A score is assigned depending on the completeness and quality of reporting. Scores increase as more criteria are met and considerations addressed. The “How to Rate” section for each item includes details about assessment criteria and considerations specific to the item. (see instruction)

1. The overall objective(s) of the guideline is (are) specifically described.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

2. The health question(s) covered by the guideline is (are) specifically described.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

4. The guideline development group includes individuals from all the relevant professional groups.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

5. The views and preferences of the target population (patients, public, etc.) have been sought.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

6. The target users of the guideline are clearly defined.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

7. Systematic methods were used to search for evidence.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

8. The criteria for selecting the evidence are clearly described.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

9. The strengths and limitations of the body of evidence are clearly described.
   ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

10. The methods used for formulating the recommendations are clearly described.
    ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
    ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7

12. There is an explicit link between the recommendations and the supporting evidence.
    ○ 1   ○ 2   ○ 3   ○ 4   ○ 5   ○ 6   ○ 7
13. The guideline has been externally reviewed by experts prior to its publication.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

14. A procedure for updating the guideline is provided.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

15. The recommendations are specific and unambiguous.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

16. The different options for management of the condition or health issue are clearly presented.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

17. Key recommendations are easily identifiable.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

18. The guideline describes facilitators and barriers to its application.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

19. The guideline provides advice and / or tools on how the recommendations can be put into practice.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

20. The potential resource implications of applying the recommendations have been considered.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

21. The guideline presents monitoring and / or auditing criteria.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

22. The views of the funding body have not influenced the content of the guideline.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

23. Competing interests of guideline development group members have been recorded and addressed.
   ○ 1  ○ 2  ○ 3  ○ 4  ○ 5  ○ 6  ○ 7

24. Overall Assessment:
   Would you recommend these guidelines for use in practice?
   ○ Strongly recommend
   ○ Recommend (with provisos alteration)
   ○ Would not recommend
   ○ Unsure

25. Data Extractor/Reviewer:
26. **Appraiser 2:**
   - Catherine
   - Sara
   - Other (specify) : ______________________________
Appendix C. Excluded Studies


Exclude: Not an eligible guideline


Exclude: Not an eligible population treatment


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Exclude: Not an eligible study design


Exclude: Not an eligible population treatment


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Exclude: Not an eligible population treatment

Do omega-3 fatty acids help in depression? Drug Ther Bull. 2007;45(2):9-12. EBSCO-CINAHL.

Exclude: Not an eligible study design


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Exclude: Not an eligible population treatment


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POEMs. CBT plus alternative SSRI is better than alternative SSRI alone in adolescent depression. JAAPA. 2008;21(5):58 EBSCO-CINAHL.

Exclude: Not an eligible study design


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Abbas AA. Intensive short-term dynamic psychotherapy of treatment-resistant depression: A pilot study. Depress Anxiety. 2006;23(7):449-52. OVID-Embase. Exclude: Not an eligible study design


Abt, KL. The effects of a group exercise intervention in the adjunctive treatment of depression Abt. 2006. OVID-PsycINFO. Exclude: Not an eligible study design


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Albin, J.I. A study measuring the effectiveness of cognitive/psychosocial intervention with a life-threatening illness: My thoughts, my illness, my life 1998. OVID-PsycINFO. Exclude: Not an eligible study design


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Excluded - Systematic review - relevant topic, citations cross-matched

Exclude: Not an eligible population treatment

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AstraZeneca. A multicenter, double-blind, randomized, parallel-group, placebo-controlled phase III study of the efficacy and safety of quetiapine fumarate extended-release (SEROQUEL XR) in combination with an antidepressant in the treatment of patients with major depressive disorder with inadequate response to an antidepressant treatment (Onyx Study). CSR Study D1448C00007-Synopsis. 2007. Exclude: Not an eligible study design

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Baldree B.F. The self-statement: Cognitive mediation in affective disorder intervention strategies 1996. OVID-PsycINFO.
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Beach SR, O'Leary KD. The treatment of depression occurring in the context of marital discord. Behav Ther. 1986;17(1):43-9. OVID-PsycINFO.

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Beck AT, Hollon SD, Young JE. Treatment of depression with cognitive therapy and amitriptyline. Arch Gen Psychiatr. 1985;42(2):142-8. OVID-Embase

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Bennett, C.F. Treatment effects of acupuncture on anxiety and depression in working women University of South Carolina. 1997. EBSCO-CINAHL. Exclude: Not an eligible study design

Bennett JA. Combined thioridazine and desipramine: Early antidepressant response. Psychopharmacol. 1984;82(3):263-5. OVID-PsycINFO. Exclude: Not an eligible population treatment


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Bonnet,L.H. Effects of aerobic exercise in combination with Cognitive Therapy on self-reported depression 2006. OVID-PsycINFO.
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Boscher RJ. Running and mixed physical exercises with depressed psychiatric patients. Int J Sport Psychol. 1993;24(2):170-84. OVID-PsycINFO.
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Boyd, G.M. Effects of group therapy on levels of depression of family caregivers of patients with dementia residing in nursing homes 2006. OVID-PsycINFO
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Bristow M, Bright J. Group cognitive therapy in chronic depression: Results from two intervention studies. Behav Cognit Psychother. 1995;23(4):373-80. OVID-Embase. Exclude: Not an eligible study design


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Bulloch AG, Patten SB. Non-remission of depression in the general population as assessed by the HAMD-7 scale. Depress Anxiety. 2008;25(5):393-7. PMID:17948276 OVID-Medline. Exclude: Not an eligible population treatment


Canna,M.A. Controlled evaluation of the effects of expressive writing on subsequent cognitive behavioral group treatment with an anxious/depressed sample 2006. OVID-PsycINFO. Exclude: Not an eligible study design


Case, S.C. The effects of group therapy and exercise on depression and self-esteem in college students 2003. OVID-PsycINFO. Exclude: Not an eligible study design


Chan, E.K.H. Efficacy of cognitive-behavioral, pharmacological, and combined treatments of depression: A meta-analysis 2006. OVID-PsycINFO. Exclude: Not an eligible study design


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Chu, I.H. Effect of exercise intensity during aerobic training on depressive symptoms in initially sedentary depressed women 2008. OVID-PsycINFO. Exclude: Not an eligible study design

Chun,D.S. An assessment of support group participation on depression and adherence in veterans with hepatitis C 2002. OVID-PsycINFO. Exclude: Not an eligible study design


Church J. The application of cognitive-behavioural therapy for depression to people with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). Psychooncol. 1998;7(2):78-88. EBSCO-CINAHL. Exclude: Not an eligible study design


Clunie F. Double blind randomised controlled trial comparing moclobemide and phenelzine in treatment resistant depression. In 2001. Wiley-CCTR. Exclude: Not an eligible study design


Cohen AJ. Treatment of anergic depression in Hashimoto's thyroiditis with fluoxetine and d-amphetamine. Depression. 1993;1(2):110-4 OVID-PsyctINFO. Exclude: Not an eligible study design


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Congleton, A.B. The effect of a cognitive-behavioral group intervention on the locus of control, attributional style, and depressive symptoms of middle school students 1996. OVID-PsycINFO.
Exclude: Not an eligible study design

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Excluded - Systematic review - relevant topic, citations cross-matched

Connerley, R.C. Distant intercessory prayer as an adjunct to psychotherapy with depressed outpatients: A small-scale investigation 2003. OVID-PsycINFO.
Exclude: Not an eligible study design

Exclude: Not an eligible population treatment


Cuijpers P. Review: Relaxation better than wait-list, minimal or no treatment for depression but not as good as psychological treatments. Evid Based Ment Health. 2009;12(3):76-7. EBSCO-CINAHL. Exclude: Not an eligible study design


Cukrowicz K.C. Prevention of anxiety and depression 2008. OVID-PsycINFO. Exclude: Not an eligible study design

Cullen J.M. Testing the effectiveness of behavioral activation therapy in the treatment of acute unipolar depression 2003. OVID-PsycINFO. Exclude: Not an eligible study design

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Cunningham J. The effects of exercise and relaxation training upon psychological variables in coronary heart patients 1980. OVID-PsycINFO.
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Dana EC. A cognitive-behavioral intervention for conduct-disordered and concurrently conduct-disordered and depressed children 1998. OVID-PsycINFO.
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Di Giulio G. Therapist, client factors, and efficacy in cognitive behavioural therapy: A meta-analytic exploration of factors that contribute to positive outcome. 2010. OVID-PsycINFO. Excluded - Systematic review - relevant topic, citations cross-matched


Exclude: Not an eligible population treatment

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Dimidjian, S. Behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of major depression 2005. OVID-PsycINFO.
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Dujovne V.F. Comparison of cognitive-behavioral to pharmacological treatment of depression in prepubertal children 1994. OVID-PsycINFO. Exclude: Not an eligible study design


Eckshtain D. Combined cognitive behavioral treatment plus caregiver sessions for childhood depression 2009. OVID-PsycINFO. Exclude: Not an eligible study design

Edwards D R. A double-blind, placebo-controlled trial of lithium augmentation of antidepressants in treatment-resistant depression in elderly patients. In 1998. Wiley-CCTR. Exclude: Not an eligible study design


Ernst E. Review: St John's wort superior to placebo and similar to antidepressants for major depression but with fewer side effects. Evid Based Ment Health. 2009;12(3):78 EBSCO-CINAHL. Exclude: Not an eligible study design


Ettelson, R.G. The treatment of adolescent depression 2003. OVID-PsycINFO. Exclude: Not an eligible study design


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Flaugher M. The intervention of music on perceptions of chronic pain, depression, and anxiety in ambulatory individuals with cancer University of Alabama at Birmingham. 2002. EBSCO-CINAHL.
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Frankenburg,J.B. The effects of three experimental phenomenological techniques in treating dysthymic depression 1996. OVID-PsycINFO.
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Frothingham, S.S. The effects of an optimism-based cognitive behavioral intervention on mood and functioning in cardiac patients 2006. OVID-PsycINFO. 
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Furtado CP, Maller JJ, Fitzgerald PB. A magnetic resonance imaging study of the entorhinal cortex in treatment-resistant depression. Psychiatry Res. 2008;163(2):133-42. PMID:18511243 OVID-Medline. Exclude: Not an eligible population treatment

Furtado VA, Srihari V, Kumar A. Atypical antipsychotics for people with both schizophrenia and depression. Cochrane Database Syst Rev. 2008;(1):Art No.:CD005377. Wiley-CDSR. Excluded - Systematic review - relevant topic, citations cross-matched


Gaik,F.V. Merging east and west: A preliminary study applying spring forest qigong to depression as an alternative and complementary treatment 2003. OVID-PsycINFO. Exclude: Not an eligible study design


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Genthner GC, Friedman HL, Studley CF. Improvement in depression following reduction of upper cervical vertebral subluxation using orthospinology technique. J Vertebral Sublux Res. 2005;1-4. EBSCO-CINAHL. Exclude: Not an eligible study design


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Guelfi J D, Troy S. Sertraline in depressed patients resistant and/or intolerant to a previous treatment. In 1999 May 15; 1999. Wiley-CCTR. Exclude: Not an eligible study design


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Hagen KD, Vesper J, Ploch M. Multicenter double-blind study examining the antidepressant effectiveness of the hypericum extract LI 160. J Geriatr Psychiatry Neurol. 1994;7(Suppl):-8 PMID:7857501 OVID-Medline. Excluded


Hanson,L.M. The efficacy of three treatments for depression: Morita psychotherapy, dietary brain-chemistry treatment, and the combination of morita psychotherapy/brain-chemistry treatment as compared to no-treatment control 2002. OVID-PsycINFO. Exclude: Not an eligible study design


Harden,J.A.T. Effect of movement group therapy on depression, morale and self-esteem in aged women University of Texas at Austin. 1989. EBSCO-CINAHL. Exclude: Not an eligible study design


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Jamison,C.S.‘. Outcome, process, and client variables in cognitive bibliotherapy with depressed adults 1994. OVID-PsycINFO. Exclude: Not an eligible study design


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Kaplan EM'. Efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors: An open-label, uncontrolled study. Clin Ther. 2002;24(7):1194-200. OVID-PsycINFO.
Exclude: Not an eligible study design

OVID-Embase.
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Klein,R.A. Expectancy enhancement as a precursor to cognitive therapy for depression: A pilot investigation 2009. OVID-PsycINFO. Exclude: Not an eligible study design


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Kovach-Anta, C.M. The effects of physical activity on levels of depression, anxiety, and hypochondriasis in the elderly 1998. OVID-PsycINFO. Exclude: Not an eligible study design


Kramlinger KG, Post RM. The addition of lithium to carbamazepine. Antidepressant efficacy in treatment-resistant depression. Arch Gen Psychiatr. 1989;46(9):794-800. Wiley-CCTR. Exclude: Not an eligible population treatment


Kronsnoble, K.M. Psychological effects of habitual aerobic exercise on cardiac patients 1996. OVID-PsycINFO. Exclude: Not an eligible study design


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Lander,R. The effect of aerobic exercise on obsessive compulsive disorder, anxiety, and depression 2005. OVID-PsycINFO.
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C-83


Legrand FD, Mille CR. The effects of 60 minutes of supervised weekly walking (in a single vs. 3-5 session format) on depressive symptoms among older women: Findings from a pilot randomized trial. Ment Health Phys Activ. 2009;2(2):71-5. OVID-Embase. Exclude: Not an eligible population treatment

Legrand F, Heuze JP. Antidepressant effects associated with different exercise conditions in participants with depression: A pilot study. J Sport Exerc Psychol. 2007;29(3):348-64. OVID-PsycINFO. Exclude: Not an eligible population treatment


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Louis M, Kowalski SD. Use of aromatherapy with hospice patients to decrease pain, anxiety, and depression and to promote an increased sense of well-being. Am J Hospice Palliat Care. 2002;19(6):381-6. EBSCO-CINAHL.
Exclude: Not an eligible population treatment

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Luciano J.S Jr. Neural network modeling of unipolar depression: Patterns of recovery and prediction of outcome 1996. OVID-PsycINFO. Exclude: Not an eligible study design


Mahoney, S.H. Depression, anxiety, and stress among the elderly: A comparison of treatment outcome between two cognitive-behavioral interventions 1998. OVID-PsycINFO. Exclude: Not an eligible study design
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Martin E, Martin S. IPT for treatment-resistant depression. In 2006. Wiley-CCTR.
Exclude: Not an eligible study design

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OVID-Embase.
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McCaffrey R. The effect of healing gardens and art therapy on older adults with mild to moderate depression. Holist Nurs Pract. 2007;21(2):79-84. EBSCO-CINAHL. Exclude: Not an eligible study design


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Miller L, Weissman M. Interpersonal psychotherapy delivered over the telephone to recurrent depressives: A pilot study. Depress Anxiety. 2002;16(3):114-7. PMID:12415535 Exclude: Not an eligible population treatment


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Moldenhauer Z. Adolescent depression: A primary care pilot intervention study 2004. OVID-PsycINFO.

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Moore J.D. The effectiveness of bright light treatment on depression in an HIV population 2009. OVID-PsycINFO.

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Myskja A, Nord PG. "The day the music died": A pilot study on music and depression in a nursing home. Nord J Music Ther. 2008;17(1):30-40. EBSCO-CINAHL. Exclude: Not an eligible study design


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Naylor E.V. A five-minute bibliotherapy prescription as a physician-delivered treatment for depression 2008. OVID-PsycINFO.
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Neidig J.L. Aerobic exercise training: Effects on depressive symptoms in HIV-infected adults Ohio State University. 1998. EBSCO-CINAHL.
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Nelson, M.K. Meta-analysis: Hypnotherapy/cognitive-behavioral therapy and its efficacy on depression compared to pharmacotherapy 2002. OVID-PsycINFO.  
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Nemets B, Osher Y, Belmaker RH. Omega-3 fatty acids and augmentation strategies in treating resistant depression. Essential Psychopharmacol. 2004;(6):59-64. Exclude: Not an eligible study design  
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Nguyen,S.D. Simultaneous technique of exercise and psychotherapy (STEP) as an adjunct to multidisciplinary treatment in acute inpatient psychiatric hospitalized older adults with depressive symptoms 2008. OVID-PsycINFO.
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Nitkin-Kaner,Y. Relationships between expressive writing about traumatic events and reduction in depressive symptomatology 2009. OVID-PsycINFO.
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Pendola, D.P. Effects of scientific weight training and muscle building nutrition on self-reports of mild to moderate depression. 1996. OVID-PsycINFO. Exclude: Not an eligible study design


OVID-Embase. Exclude: Not an eligible study design


Price CS, Taylor FB. A retrospective chart review of the effects of modafinil on depression as monotherapy and as adjunctive therapy. Depress Anxiety. 2005;29(1):149-53. Exclude: Not an eligible population treatment


Ragan,J.D. Excessive reassurance-seeking, interpersonal rejection, rejection sensitivity and depressive symptoms: An intervention focusing on mediating mechanisms 2006. OVID-PsycINFO. Exclude: Not an eligible study design


Exclude: Mixed antidepressants:some failed on SSRI

Randall F. Differences between Christian Cognitive Behavioral Therapy and cognitive behavioral therapy as measured by depression and resiliency. 2004. OVID-PsycINFO.
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Exclude: Mixed antidepressants:some failed on SSRI

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Rapp, S.L. A cognitive-behavioral treatment of older medical inpatients with depressive symptoms. 1998. OVID-PsycINFO.
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C-121


Ravindran L, Lam R, Chaput Y and others. Impact of low vs. high dose olanzapine or risperidone on outcome and side effects in non-psychotic treatment resistant depression. In 2006. Wiley-CCTR. Exclude: Not an eligible study design


Ree MJ, Craigie MA. Outcomes following mindfulness-based cognitive therapy in a heterogeneous sample of adult outpatients. Behav Change. 2007;24(2):70-86. OVID-PsycINFO. Exclude: Not an eligible study design


Rene R. The efficacy of a portable HRV feedback device in conjunction with mental health treatment of clients with major depressive disorder enrolled in a county welfare-to-work program 2008. OVID-PsycINFO. Exclude: Not an eligible study design


Ritchie,L.G. Group telepsychotherapy for reducing depression: An exploratory study 2008. OVID-PsycINFO. Exclude: Not an eligible study design


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Rohon, N.A. Analysis of efficacy and mediators of outcome in minimal-contact cognitive bibliotherapy used in the treatment of depressive symptoms 2003. OVID-PsycINFO.
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Schening, L.J. Refractory depression treatment options: A meta-analysis. 2004. OVID-PsycINFO.
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OVID-Embase.
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Schultz, C.L. The effect of cognitive group therapy in 
the treatment of depression among residents of senior 
communities 1996. OVID-PsycINFO. 
Exclude: Not an eligible study design

study of adjunctive modafinil in patients with 
sedation related to serotonergic antidepressant 
PMID:15367049 OVID-Medline. 
Exclude: Not an eligible study design

Aripiprazole augmentation of selective serotonin or 
serotonin norepinephrine reuptake inhibitors in the 
treatment of major depressive disorder. Prim 
Exclude: Not an eligible study design

Sustained response to open-label venlafaxine in drug- 
resistant major depression. J Clin Psychopharmacol. 
Exclude: Not an eligible study design

Schweizer E, Rickels K, Amsterdam JD, et al. What 
constitutes an adequate antidepressant trial for 
PMID:2403998 OVID-Medline. 
Exclude: Mixed antidepressants:some failed on SSRI

Schweizer E, Rynn M, Mandos LA, et al. The 
antidepressant effect of sertraline is not enhanced by 
dose titration: Results from an outpatient clinical 
PMID:11354235 OVID-Medline. 
Exclude: Not an eligible study design

Scogin F, Jamison C, Gochneau K. Comparative 
efficacy of cognitive and behavioral bibliotherapy for mildly and moderately 
PMID:2738212 OVID-Medline. 
Exclude: Not an eligible study design

Scogin F, Jamison C, Davis N. Two-year follow-up 
of bibliotherapy for depression in older adults. J 
PMID:2254516 OVID-Medline. 
Exclude: Not an eligible study design

psychotherapies for depression in older adults. Clin 
Psychol Sci Pract. 2005;12(3):222-37. OVID- 
Embace. 
Excluded - Systematic review - relevant topic, 
citations cross-matched

Scogin F, Hamblin D, Beutler L. Bibliotherapy for 
depressed older adults: A self-help alternative. 
Exclude: Not an eligible population treatment

Scott AI, Freeman CP. Edinburgh primary care depression study: treatment outcome, patient 
satisfaction, and cost after 16 weeks. Br Med J. 
1992;304(6831):883-7. PMID:1392754 OVID- 
Medline. 
Exclude: Not an eligible population treatment

Scott C, Tacchi MJ, Jones R, et al. Acute and one- 
year outcome of a randomised controlled trial of brief 
cognitive therapy for major depressive disorder in 
PMID:9337947 OVID-Medline. 
Exclude: Not an eligible population treatment

cognitive therapy for depression: A pilot study in 
OVID-Embace. 
Exclude: Not an eligible study design

Scott J. Chronic depression: Can cognitive therapy 
succeed when other treatments fail? Behav 
Exclude: Not an eligible population treatment

Scott J, Moon CA, Blacker CV, et al. A. I. F. Scott 
& C. P. L. Freeman's "Edinburgh Primary Care 
Depression Study. Br J Psychiatr. 1994;164(3):410- 
5. PMID:8199795 OVID-Medline. 
Exclude: Not an eligible study design

Scott J, Teasdale JD, Paykel ES, et al. Effects of 
cognitive therapy on psychological symptoms and 
social functioning in residual depression. Br J 
Psychiatr. 2000;177:440-6. PMID:11059998 OVID-

Medline. 
Exclude: Mixed antidepressants:some failed on SSRI

Scott J, Palmer S, Paykel E, et al. Use of cognitive 
therapy for relapse prevention in chronic depression. 
Exclude: Not an eligible population treatment

Scott MJ, Stradling SG. Group cognitive therapy for 
depression produces clinically significant reliable 
change in community-based settings. Behav 
Exclude: Not an eligible population treatment

Scott,T.M. Treating adult depression in rural areas 
through videoconferencing 2009. OVID-PsycINFO. 
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Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. Arch Gen Psychiatr. 2010;67(12):1256-64. PMID:21135325 OVID-Medline. Exclude: Not an eligible population treatment


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Shelton RC, Tohen M, Stahl S, et al. The study of olanzapine plus fluoxetine in treatment-resistant major depressive disorder without psychotic features. Schizophr Res. 2000;Number 1 - Special Issue: Wiley-CCTR. Exclude: Not an eligible study design


Shelton RC. Symbyax® (olanzapine and fluoxetine HCl) for the acute treatment of treatment-resistant depression. Psychiatr Times. 2009;20-7. EBSCO-CINAHL. Exclude: Mixed antidepressants:some failed on SSRI


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Stevinson C. Preliminary results suggest that yoga can alleviate depression. Focus Alternative Compl Ther. 2001;6(1):27-8. OVID-AMED. Exclude: Not an eligible study design


Sudweeks C. Effects of cognitive group hypnotherapy in the alteration of depressogenic schemas. Sudweeks. 1998. OVID-PsycINFO. Exclude: Not an eligible study design


Excluded - Systematic review - relevant topic, citations cross-matched


Exclude: Not an eligible population treatment


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Teasdale JD, Fennell MJV. Immediate effects on depression of cognitive therapy interventions. Cognit Ther Res. 1982;6(3):343-52. OVID-Embase

OVID-Embase.

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OVID-Embase.

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Terao T. Lack of urinary side-effects with nefazodone as compared to other newer antidepressants. Hum Psychopharmacol Clin Exp. 1998;13(4):245-6. OVID-PsycINFO.

Exclude: Not an eligible study design


Exclude: Not an eligible population/treatment


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Tutty S. Evaluating the effectiveness of teletherapy in rural depressed adults Tutty. 2008. OVID-PsycINFO. Exclude: Not an eligible study design


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Excluded: Mixed antidepressants: some failed on SSRI

Vitiello B. Combined fluoxetine with cognitive-behavioral therapy vs. monotherapy in the treatment of adolescents with major depressive disorder. Dir Psychiatr. 2007;27(2):73-82. OVID-PsycINFO.

Excluded - Systematic review - relevant topic, citations cross-matched


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Weiss J.C. A comparison of cognitive group therapy to life review group therapy with older adults Weiss. 1994. OVID-PsycINFO.
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Wheatley D. Side-effects are no problem with St John's wort in depression. Prim Care Psychiatr. 2002;8(1):31-3. Exclude: Not an eligible study design

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Wierzbicki M, Bartlett TS. The efficacy of group and individual cognitive therapy for mild depression. Cognit Ther Res. 1987;11(3):337-42. OVID-Embase.
Exclude: Not an eligible population treatment

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Wilkinson P. In adolescents with SSRI resistant depression, CBT/combined treatment is most effective in those with comorbid disorders. Evid Based Ment Health. 2009;12(4):108 EBSCO-CINAHL.
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Yury,C.A. Analysis of empirical research on augmentation strategies for unipolar depression Yury. 2009. OVID-PsycINFO.
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Zerka Yoo,C. Hapkido vs. yoga: Analysis of choice, persistence and psychological benefits Zerka Yoo. 2008. OVID-PsycINFO. Exclude: Not an eligible study design


