Comparative Effectiveness Review
Number 62

Effective Health Care Program

Treatment for Depression After Unsatisfactory Response to SSRIs

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.[1,2] Depression exerts a negative impact on physical health; it reduces adherence to medical treatment,[3] reduces participation in preventive activities,[4] and increases the likelihood of risk factors such as obesity,[5] smoking,[6] and sedentary lifestyles.[7] MDD may be associated with immune dysfunction[8-11] and cardiovascular disease,[12-15] endocrine and neurological diseases, and a general increase in chronic disease incidence.[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.[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.[18]

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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

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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.[19] Up to one-third of persons taking antidepressant medications will develop recurrent symptoms of depression while on therapy.[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[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.[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 paroxetin) 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[23] to assess randomized controlled and controlled clinical trials. Studies were evaluated for adequacy of collecting and reporting harms using the McHarm scale.[24,25] The AGREE II instrument was used to assess the methodological quality of the CPG.[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).[27] 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)[30,34,37,39,48,49,51-53,55,59-61,63,65,69,71,72] 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,[69] venlaxafine,[39] or paroxetine.[53] The remaining eight studies (nine publications) evaluated head-to-head comparison following switching from: (1) citalopram to venlaxafine, bupropion, sertraline, or cognitive behavior therapy (CBT);[34,59,63]
(2) paroxetine to venlaxafine;[61] (3) fluoxetine to olanzapine or mianserin;[37,71,72] or, (4) from an SSRI to duloxetine (tapering methods).[52,55] 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.[69] 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)[28-33,35-38,40-51,54,57-64,68-74,76-78,80-87] 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)[28,29,35-37,44,54,57,58,61-63,68,69,72,74,76,78] determined failure of response to the SSRI prospectively and 16 retrospectively (18 publications).[31-33,38,40-43,45-47,64,70,71,73,77,80,84] No studies evaluated subjects specifically for failed response to fluvoxamine alone.

All but one study[59,62,63] 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[31,32,47,62,68] 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),[37,44,57,72] lithium,[47,61,68,74] buspirone,[41,46,59,62,63,70,80] mianserin,[69,72] and pindolol.[42,45] Five studies evaluated the use of nonpharmacological interventions including CBT,[43,59] dialectical behavior therapy,[78] interpersonal therapy,[83,85,87] and exercise.[77] 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,[28,29,35-37,41,44,46,50,54,57,58,61,64,69-72,80-82,84] ten (13 publications) by non-industry sources,[38,43,47,59,62,63,68,74,77,78,83,85,87] and one by both.[33] 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, ariprazole, 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 antipyschotics, 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 (n=832)[35,47,59,62,68,75] for which there were treatment arms that compared combination therapies with each other. All but one study[75] were RCTs. Women were the majority in all studies, and age ranges varied from 37 to 59 years. Only two studies reported racial composition,[59,62] and these subjects were predominately white. Two studies[35,75] 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,[89,92,93,96-101] and a second trial of ages 8 to 18.[90] 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.[89,92,93,96-101] 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.[90]

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,[30,37,41,46,51,64,66,68-70,80] and one for adolescents.[89,92,93] 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.[18,102-133] Seven CPGs were specific only to adolescents,[18,126-131] 18 CPGs were for adults alone,[102,103,105,107-111,113-117,119,121,123-125] and 2 CPGs were applicable to both.[132,133] Four CPGs for adults[107,109,116,119] and three for adolescents[18,127,130] did not provide any recommendations for patients with previous inadequate responses. Five of the 27 guidelines included patients with dysthymia and subsyndromal depression[103,123,126,132,133] 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 CONSORT[134] (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.

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