

AHRQ Comparative Effectiveness Review Surveillance Program

CER # 62: Treatment of Depression after Unsatisfactory Response to SSRIs

Original release date: April 2012

Surveillance Report: January 2013

Key Findings:

- All conclusions are up to date.

Summary Decision

This CER's priority for updating is **Low**

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1. Introduction

Comparative Effectiveness Review (CER) #62 was originally released in April, 2012.¹ Therefore, our surveillance assessment began in October, 2012. At that time, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed. We also conducted an updated electronic literature search. Every month since the CER's original release, we received any applicable warnings from the U.S. Food and Drug Administration (FDA), Health Canada, and UK Medicines and Healthcare products Regulatory Agency (MHRA) on the included medications.

2. Methods

2.1 Literature Searches

We conducted an initial limited literature search covering January 1, 2011 to October 9, 2012, using the identical search strategy used for the original report. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology, and Journal of the American Academy of Child and Adolescent Psychiatry). The specialty journals were those most highly represented among the references for the original report. This search resulted in 103 titles / abstracts to review. Appendix A includes the search strategy.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER.

2.3 Expert Opinion

We shared the conclusions of the original report with eleven experts in the field (including the original project leader, original technical expert panel (TEP) members, and original peer reviewers, to request their assessment of the need to update the report and their recommendations of any relevant new studies. Three subject matter experts and the original project lead responded back. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

The authors of the original CER undertook qualitative synthesis separately for adults and adolescents, dividing studies by a) monotherapy versus monotherapy, b) monotherapy versus combined therapy, and c) combined therapy versus combined therapy. Adverse events including

headache, gastro-intestinal problems, and sexual dysfunction were presented. We looked for both quantitative and qualitative signals.

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that includes the key questions, the original conclusions, the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. We categorized whether the conclusions need updating using a 4-category scheme:

- Original conclusion is still valid and this portion of the CER does not need updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is probably out of date and this portion of the CER may need updating
- Original conclusion is out of date.

We used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a

black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 103 titles. After title and abstract review, we selected 15 for full text review. The remaining titles / abstracts were rejected because they were editorials, letters, animal studies, individual case reports, did not include topics of interest or were already included in the original CER. In addition, two experts advised us of a new (2011) guideline on SSRI treatment of adults in primary care.²

Upon full text review, nine articles were rejected because they did not meet the original CER inclusion criteria. For example, some were descriptions of utilization patterns, some reviewed studies already included in the CER, and some studies had no control or comparison group. The remaining six studies were abstracted into an evidence table (Appendix B).³⁻⁸

3.2 Expert Opinion

We shared the conclusions of the original report with eleven experts in the field (including the original project leader, original technical expert panel (TEP) members, and original peer reviewers) to request their assessment of the need to update the report and their recommendations of any relevant new studies. The original CER authors and three subject matter experts responded.

The three experts felt all the conclusions were either up to date or did not know. They did not suggest that any conclusion might be out of date.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, and the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update.

The few new studies we identified supported the conclusions of the original CER. The new guideline supported the guidelines described in the original CER. Thus, there is no need to update the CER at this time.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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?				
<u>Subsyndromal and dysthymia in adults</u> One study evaluated subjects with subsyndromal depression and another with dysthymia; both of these studies showed no differences between groups when comparing monotherapy or combined therapy treatments.	No new studies identified.	NA	EPC investigator did not know. Three experts felt the conclusion was up to date.	Conclusion is up to date.
<u>Monotherapy Versus Monotherapies in Adults</u> Twelve studies (18 publications) compared monotherapy interventions. All participants (n=2,611) had MDD. Three of the studies involved dose escalation of sertraline, venlafaxine, or paroxetine. The remaining studies 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). 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	No new studies identified.	NA	EPC investigator did not know. Three experts felt the conclusion was up to date.	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>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.</p> <p>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).</p>				
<p><u>Monotherapies Versus Combined Therapies in Adults</u></p> <p>A total of 33 studies evaluated monotherapy relative to combined therapies. Participants were all diagnosed with MDD. The majority of studies 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</p>	<p>A new systematic review (Cooper, 2011) on adults age 55 and over included 14 trials on SSRI alone vs augmentation with risperidone, aripiprazole, citalopram, bupropion, lithium, or phenelzine. Overall response rate for augmentation was 52%. Only lithium augmentation was</p>	NA	EPC investigator did not know. Three experts felt the conclusion was up to date.	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>new treatment in at least one study arm.</p> <p>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).</p> <p>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.</p>	<p>assessed in more than 2 trials</p> <p>We identified an RCT comparing SSRI alone vs SSRI + augmentation with lamotrigine (Barbee, 2011). Outcomes did not differ between the groups at 10 weeks. We found a Chinese RCT of SSRI alone vs augmentation with risperidone, valproate, buspirone, trazadone, or thyroid hormone (Fang, 2011). Remission rates did not differ among arms at 8 weeks. We identified a follow-up where patients not responding to augmentation with 2 mg aripiprazole had dose increased to 5 mg (Mischoulon, 2012). Outcomes did not differ from those of placebo group at 4 weeks. Finally, we found an RCT (Trivedi, 2011) comparing augmentation of SSRI with 2 different doses of exercise. There were significant improvements at 12 weeks for both groups, with no differential group effect.</p>			
<u>Combined Therapies Versus Combined</u>	No new studies identified.	NA	EPC investigator did not know. Three experts felt the	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p><u>Therapies in Adults</u></p> <p>There were six studies (n=832) for which there were treatment arms that compared combination therapies. All but one study were RCTs. There was no certainty of a difference between any combination therapy, including a dose escalation, for the added augmenting agent.</p> <p>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.</p>			conclusion was up to date.	
<p><u>Treatment in Adolescents</u></p> <p>Two trials evaluated therapies in children and adolescents; 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. 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 had low risk of bias and showed no differences between the medication groups. There was a statistically significant difference in favor of including CBT for all outcomes. The second trial evaluated a dose escalation of fluoxetine in a</p>	A long term follow-up of TORDIA was identified (Vitiello, 2011). Treatment assignment did not predict outcomes (remission or time to remission) at 48 and 72 weeks follow-up.	NA	EPC investigator felt the conclusion is still valid. Two experts felt the conclusion was up to date. One expert did not know.	Conclusion is up to date.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
small sample, and was suggestive of some benefit to the higher dose, but the study was underpowered to detect a difference. 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 for both adults and adolescents were predominately derived from RCTs. 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	The new trials reported no difference between groups in any adverse event.	No warnings from Health Canada or MHRA. In May, 2012, Health Canada issued a labeling update for escitalopram: this drug should not be used in patients with long QT syndrome or QT interval prolongation. 10 mg per day is the maximum dose for patients 65 or older.	EPC investigator did not know. Two experts felt the conclusion was up to date. One expert did not know.	Conclusion still valid.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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 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.	The new studies mentioned above (key question one) supported the initial CER findings.	NA	EPC investigator did not know. Two experts felt the conclusion was up to date. One expert did not know.	Conclusion is up to date.
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	Both the original EPC investigator and one expert suggested one new CPG that supports those included in the original CER.	NA	EPC investigator felt the conclusion is still valid. Two experts felt the conclusion was up to date. One expert did not know.	Conclusion still valid.

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
<p>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.</p>				

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Some adolescent guidelines cited adult evidence as the evidentiary basis for suggesting treatment strategies.				

Legend: CBT: Cognitive Behavior Therapy; CPG: Clinical Practice Guidelines; MDD: Major Depressive Disorder; SCEPC: Southern California Evidence-based Practice Center

References

1. Santaguida P, MacQueen G, Keshavarz H, et al. Treatment for Depression After Unsatisfactory Response to SSRIs. Comparative Effectiveness Review No. 62. (Prepared by McMaster University Evidence-based Practice Center under Contract No. HHSA 290 2007 10060 I.) AHRQ Publication No. 12-EHC050-EF Agency for Healthcare Research and Quality. Rockville, MD: April 2012.
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Appendices

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:

MEDLINE VIA OVID – 1/1/2011-10/9/2012

LANGUAGE:

English

SEARCH STRATEGY:

- 1 dysthm*.tw.
- 2 limit 1 to (english language and yr="2011 - 2012")
- 3 (subclinical adj2 depressi*).tw. 176
- 4 limit 3 to (english language and yr="2011 - 2012")
- 5 (subsyndromal adj2 depressi*).tw. 207
- 6 limit 5 to (english language and yr="2011 - 2012")
- 7 (subthreshold adj2 depressi*).tw. 233
- 8 limit 7 to (english language and yr="2011 - 2012")
- 9 (subdiagnostic adj2 depressi*).tw.
- 10 limit 9 to (english language and yr="2011 - 2012")
- 11 Depression/
- 12 limit 11 to (english language and yr="2011 - 2012")
- 13 depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
- 14 limit 13 to (english language and yr="2011 - 2012")
- 15 2 or 4 or 6 or 8 or 10 or 12 or 14
- 16 serotonin uptake inhibitors/ or citalopram/ or fluoxetine/ or fluvoxamine/ or paroxetine/ or sertraline/
- 17 (citalopram or celexa or cipramil or dalsan or recital or emocal or sepram or seropram).mp.
- 18 (escitalopram or es citalopram or lexapro or cipralext or esertia).mp.
- 19 (fluoxetine or prozac or fontex or seromex or seronil or sarafem or fluctin or fluox or lovan).mp.
- 20 (fluvoxamine or luvox or fevarin or faverin or dumyrox or favoxil or movox).mp.
- 21 (paroxetine or paxil or seroxat or sereupin or aropax or deroxat or rexetin or xetanor or paroxat).mp.
- 22 (sertraline or zoloft or lustral or serlain).mp.
- 23 ssri?.mp.
- 24 selective serotonin reuptake inhibit*.tw.
- 25 symbyax.mp.
- 26 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
- 27 Drug Resistance/
- 28 treatment failure/
- 29 Retreatment/
- 30 ((difficult or hard) adj3 treat).tw.
- 31 augment*.tw.
- 32 nonrespon*.tw.
- 33 non-respon*.tw.
- 34 switch*.tw.

35 ((insufficient or inadequate or incomplete) adj3 respon*).tw.
 36 (ssri? adj3 (resist* or fail* or respon* or refractory)).tw.
 37 (partial adj3 respon*).tw.
 38 ((combination or adjunct*) adj3 (therap* or drug? or treat*)).tw.
 39 ((treat* or therapy or drug) adj4 (resist* or fail*)).tw.
 40 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
 41 ((treatment resistant or refractory) adj3 depressi*).tw.
 42 15 and 40
 43 41 or 42
 44 15 and 26
 45 43 or 44
 46 *depression/ or *depressive disorder/ or *depressive disorder, major/ or *dysthymic disorder/
 47 2 or 4 or 6 or 8 or 10
 48 46 or 47
 49 5-Hydroxytryptophan/
 50 phototherapy/
 51 light therapy.tw.
 52 exp Exercise/ae, th
 53 exp Exercise Therapy/
 54 exp Acupuncture Therapy/
 55 exp Massage/
 56 Relaxation Therapy/
 57 exp vitamins/
 58 Hypericum/
 59 john* wort.tw.
 60 deplin.tw.
 61 methylfolate.tw.
 62 Folic Acid/
 63 S-Adenosylmethionine/
 64 "SAM-e".tw.
 65 exp Fatty Acids, Omega-3/
 66 Cognitive Therapy/
 67 Crocus/
 68 Tryptophan/
 69 exp Inositol/
 70 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or
 64 or 65 or 66 or 67 or 68 or 69
 71 limit 70 to yr="2011 - 2012"
 72 limit 48 to yr="2011 - 2012"
 73 (harm? or adverse or "side effect?").tw.
 74 (adjunct* or augment*).tw.
 75 73 or 74
 76 72 and 75 7
 77 exp *antidepressive agents/ae, to
 78 76 or 77

79 45 and 71 and 72

80 76 or 78 or 79

81 limit 80 to (english language and yr="2011 - 2012")

82 animals/ not (animals/ and humans/)

83 81 not 82 1

84 (comment or editorial).pt.

85 83 not 84

TOTAL NUMBER OF RESULTS: 988

**TOTAL AFTER REMOVAL OF INTERNAL DUPLICATES AND SELECTED
NON-RELEVANT MATERIAL: 866**

FILTERED IN ENDNOTE TO LIMIT TO THE FOLLOWING JOURNALS:

Annals of Internal Medicine

BMJ

JAMA

Lancet

New England Journal of Medicine

American Journal of Psychiatry

Archives of General Psychiatry

J Clinical Psychiatry

J Clinical Psychopharmacology

J American Academy of Child & Adolescent Psychiatry.

TOTAL AFTER FILTERING FOR SPECIFIED JOURNALS: 103

Appendix B. Evidence Table

Author, year	Study design	Country	Population	Intervention category	Specific interventions	Setting / Duration	Outcomes	AEs	Special pops
Barbee, 2011 ³	RCT	US	96 adults who failed open label trial of paroxetine or paroxetine extended release	Augmentation	Lamotrigine vs placebo	Multicenter outpatient / 10 weeks	Change in MADRS, HDRS-17, and CGI did not differ significantly between drug & placebo groups	No differences in AEs between groups	Baseline severity correlated with drug response, i.e. more severe depression associated with greater decrease in depression in drug group
Cooper, 2011 ⁴	Systematic review	Various	Adults age 55 or over	Augmentation, monotherapy	Risperidone, aripiprazole, citalopram, bupropion, lithium, phenelzine, SSRIs	14 trials, from 2 weeks to 55 weeks	Overall response rate for all active tx was 52%. Only lithium augmentation was assessed in more than two trials.	Not discussed	Only included studies of age 55+
Fang, 2011 ⁵	RCT	China	225 adults	Augmentation	Risperidone, Valproate, Buspirone, Trazodone, Thyroid hormone	Multicenter outpatient / 8 weeks	No statistical difference among treatment arms in remission rates	No statistical difference among arms in AEs. No serious AEs reported	None

Author, year	Study design	Country	Population	Intervention category	Specific interventions	Setting / Duration	Outcomes	AEs	Special pops
Mischoulon, 2012 ⁶	RCT	US	221 adults	Augmentation / dose increase	Increased dose to 5 mg/day for those who did not respond to initial augmentation with 2 mg aripiprazole	Multicenter outpatient / 4 weeks	No statistical difference between 5 mg group and placebo group	No statistical difference between 5 mg group and placebo group	Parent study is Fava, 2009, 2010
Trivedi, 2011 ⁷	RCT	US	126 adults 18 to 70 years old	Augmentation with exercise	Exercise expending 16 kcal per kg per week (KKW) vs exercise of 4 KKW	Cooper Institute, 12 weeks	There were significant improvements over time for both groups combined without differential group effect.	Not reported	Men, regardless of family history of mental illness, and women without a family history of mental illness had higher remission rates with higher dose exercise
Vitiello, 2011 ⁸	RCT, long term f/u of TORDIA	US	334 adolescents	Augmentation or switch, with or without CBT	A) switch to venlafaxine, B) switch to another SSRI, C) switch to venlafaxine + CBT, D) switch to	Multicenter outpatient, 48 and 72 weeks	Initial tx assignment did not predict remission or time to remission	Not reported	Patients with more severe depression, greater dysfunction, and alcohol or drug use at baseline

Author, year	Study design	Country	Population	Intervention category	Specific interventions	Setting / Duration	Outcomes	AEs	Special pops
					another SSRI + CBT, discharged to "community care" after 24 weeks				were less likely to remit.

Legend: CBT: Cognitive Behavior Therapy; CPG: Clinical Practice Guidelines; MDD: Major Depressive Disorder; RCT: Randomized Controlled Trial; SCEPC: Southern California Evidence-based Practice Center

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Treatment for Depression After Unsatisfactory Response to SSRIs

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
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?			
<u>Subsyndromal and dysthymia in adults</u> One study evaluated subjects with subsyndromal depression and another with dysthymia; both of these studies showed no differences between groups when comparing monotherapy or combined therapy treatments.	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>
<u>Monotherapy Versus Monotherapies in Adults</u> Twelve studies (18 publications) compared monotherapy interventions. All participants (n=2,611) had MDD. Three of the studies involved dose escalation of sertraline,	<input type="checkbox"/>	New Evidence:	<input type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
<p>venlafaxine, or paroxetine. The remaining studies 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). 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</p>			

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<p>monotherapies are equivalent in their treatment effects.</p> <p>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).</p>			
<p><u>Monotherapies Versus Combined Therapies in Adults</u></p> <p>A total of 33 studies evaluated monotherapy relative to combined therapies. Participants were all diagnosed with MDD. The majority of studies 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.</p> <p>The majority of studies showed no certainty of any difference for any monotherapy treatment, relative to the comparator combined therapy, for the outcomes of</p>	<div data-bbox="753 976 814 1032" data-label="Image"></div>	<p>New Evidence:</p>	<div data-bbox="1766 976 1827 1032" data-label="Image"></div>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
<p>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). 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.</p>			
<p><u>Combined Therapies Versus Combined Therapies in Adults</u></p> <p>There were six studies (n=832) for which there were treatment arms that compared</p>	<input data-bbox="758 1279 814 1339" type="checkbox"/>	<p>New Evidence:</p>	<input data-bbox="1766 1279 1822 1339" type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
<p>combination therapies. All but one study were RCTs. There was no certainty of a difference between any combination therapy, including a dose escalation, for the added augmenting agent.</p> <p>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.</p>			
<p>Treatment in Adolescents</p> <p>Two trials evaluated therapies in children and adolescents; 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. 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 had low risk of bias and showed no differences between the medication groups. There was a statistically significant difference in favor</p>	<div data-bbox="753 914 814 971" data-label="Image"></div>	<p>New Evidence:</p>	<div data-bbox="1761 914 1822 971" data-label="Image"></div>

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<p>of including CBT for all outcomes. 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.</p> <p>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.</p>			
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?			
<p>Harms for interventions for both adults and adolescents were predominately derived from RCTs. 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.</p> <p>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</p>	<div data-bbox="753 1122 814 1182" data-label="Image"></div>	<p>New Evidence:</p>	<div data-bbox="1761 1122 1822 1182" data-label="Image"></div>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
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 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	<input data-bbox="758 1101 814 1156" type="checkbox"/>	New Evidence:	<input data-bbox="1766 1101 1822 1156" type="checkbox"/>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Is there new evidence that may change this conclusion?	Do Not Know
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?			
<p>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</p>	<div data-bbox="753 1024 814 1081" data-label="Image"></div>	<p>New Evidence:</p>	<div data-bbox="1761 1024 1822 1081" data-label="Image"></div>

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<p>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.</p>			

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Are there new data that could inform the key questions that might not be addressed in the conclusions?			