Table A-5. Comparative effectiveness of second-generation antidepressants in the pharmacologic treatment of adult depression

| Original Key Questions/Conclusions | Updated Key Questions/Conclusions (2011-2012) | 2009 Prediction | Concordance |
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| Comparative Effectiveness of Second-Generation Antidepressants in the Pharmacologic Treatment of Adult Depression (Original report date - Jan 2007[9](#_ENREF_9) and Update report date - Dec 2011[10](#_ENREF_10)) |
| Key Question 1a. - For adults with major depressive disorder (MDD), dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms? | Key Question 1a. - For adults with major depressive disorder (MDD), dysthymia, or subsyndromal depressive disorders, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms? |   |   |
| The relative risk (RR) of response was significantly greater for escitalopram than for citalopram. | Citalopram versus escitalopram (5 published studies; 1,802 patients): For patients on escitalopram the odds ratio (OR) of response was statistically significantly higher than for patients on citalopram (OR, 1.47; 95% confidence interval [CI], 1.07 to 2.01). The number needed to treat (NNT) to gain 1 additional responder at week 8 with escitalopram compared with citalopram was 13 (95% CI, 8 to 39). These results are based on metaanalyses of head-to-head trials. Results of mixed-treatment comparisons, taking the entire evidence base on second-generation antidepressants into consideration, did not confirm these findings (OR, 0.51; 95% credible interval, 0.13 to 4.14). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Fluoxetine vs. paroxetine: We did not find any statistically significant differences in effect sizes on the Hamilton Rating Scale for Depression (HAM-D) or response rates between fluoxetine and paroxetine. Paroxetine led to a higher rate of responders than fluoxetine. | Fluoxetine versus paroxetine (5 studies; 690 patients): We did not find any statistically significant differences in response rates (OR, 1.08; 95% CI, 0.79 to 1.47) between fluoxetine and paroxetine. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Fluoxetine vs. sertraline: Patients on sertraline had an additional, statistically nonsignificant treatment effect of a 0.75-point reduction (95-percent CI, –0.45-1.95) on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was significantly greater for sertraline than for fluoxetine. | Fluoxetine versus sertraline (4 studies; 940 patients): The odds ratio of response was statistically significantly higher for sertraline than for fluoxetine (OR, 1.42; 95% CI, 1.08to 1.85). The NNT to gain 1 additional responder at 6 to 12 weeks with sertraline was 13 (95% CI, 8 to 58). | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Fluoxetine vs. venlafaxine: Patients on venlafaxine had an additional, statistically nonsignificant treatment effect of a 1.31-point reduction on the HAM-D scale compared with patients on fluoxetine. The relative risk of response was significantly greater for venlafaxine than for fluoxetine. | Fluoxetine versus venlafaxine (6 studies; 1,197 patients): The odds ratio of response was statistically significantly higher for patients on venlafaxine than on fluoxetine (OR, 1.47; 95% CI, 1.16 to 1.86). | Conclusion is possibly out of date and this portion of the CER may need updating. Although we found only one new conflicting RCT, methods and inclusion criteria of new meta-analysis (Nemeroff, 2008) should be reviewed. | Fair The Nemeroff meta-analysis was reviewed but rejected for not assessing an outcome of interest.  |
| Findings from indirect comparisons yielded no statistically significant differences in response rates. The precision of some of these estimates was low, leading to inconclusive results with wide confidence intervals. | Results from direct and indirect comparisons based on 61 head-to head trials and 31 placebo-controlled trials indicate that no substantial differences in efficacy exist among second-generation antidepressants. Direct evidence from three effectiveness trials (one good) and indirect evidence from efficacy trials indicate that no substantial differences in effectiveness exist among second-generation antidepressants. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Eighteen studies indicated no statistical differences in efficacy with respect to health-related quality of life (HRQOL).  | Consistent results from 18 trials indicate that the efficacy of second generation antidepressants with respect to quality of life does not differ among drugs. | Conclusion is still valid and this portion of the CER does not need updating. New data on adverse events (suggested by one expert) is covered in key question 4.  | Good |
| Seven studies funded by the maker of mirtazapine reported that mirtazapine had a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. | Consistent results from seven trials suggest that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline. Whether this difference can be extrapolated to other second-generation antidepressants is unclear. Most other trials do not indicate a faster onset of action of one second-generation antidepressant compared with another. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| We identified no head-to-head trials for dysthymia. In placebo-controlled trials, significant differences in population characteristics make the evidence insufficient to identify differences between treatments. | No head-to-head evidence exists. Results from five placebo controlled trials were insufficient to draw conclusions about comparative efficacy. No head-to-head evidence exists. One effectiveness trial provides mixed evidence about paroxetine versus placebo; patients older than 60 showed greater improvement on paroxetine; those younger than 50 did not show any difference. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| The only head-to-head evidence for treating patients with subsyndromal depression came from a nonrandomized, open-label trial comparing citalopram with sertraline. This study did not detect any differences in efficacy. Findings from two placebo-controlled trials were insufficient to draw any conclusions about the comparative efficacy and effectiveness. | One nonrandomized, open-label trial did not detect any difference between citalopram and sertraline. Results from two placebo-controlled trials were insufficient to draw conclusions. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Key Question 1b. - If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms? | Key Question 1b. - If a patient has responded to one agent in the past, is that agent better than current alternatives at treating depressive symptoms? |   |   |
| We did not find any efficacy evidence regarding this question. | No evidence | Conclusion is still valid and this portion of the CER does not need updating. | Good |
|   | Key Question 1c. -Are there any differences in efficacy or effectiveness between immediate-release and extended-release formulations of second-generation antidepressants? |   |   |
|   | Results from two trials indicate that no differences in response to treatment exist between paroxetine IR and paroxetine CR. Two trials did not detect significant differences in maintenance of response and remission between fluoxetine daily and fluoxetine weekly. One trial reported higher response rates for venlafaxine XR than venlafaxine IR. |   | Not applicable. There was no similar KQ in the original report, and for this update the addition of this KQ yielded no important clinical differences |
| Key Question 2a. - For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (i.e., preventing relapse or recurrence)? | Key Question 2a. - For adults with a depressive syndrome that has responded to antidepressant treatment, do second-generation antidepressants differ in their efficacy or effectiveness forpreventing relapse (i.e., continuation phase) or recurrence (i.e., maintenance phase) when a patient: o Continues the drug to which they initially responded, or o Switches to a different antidepressant? |   |   |
| Three head-to-head RCTs suggest that no substantial differences exist between fluoxetine and sertraline, fluvoxamine and sertraline, and trazodone and venlafaxine, regarding relapse. Twenty-one placebo-controlled trials support the general efficacy and effectiveness of most second-generation antidepressants for preventing relapse or recurrence. No evidence exists for duloxetine. | Based on results from six efficacy trials and one naturalistic study, no significant differences exist between escitalopram and desvenlafaxine, escitalopram and paroxetine, fluoxetine and sertraline, fluoxetine and venlafaxine, fluvoxamine and sertraline, and trazodone and venlafaxine for preventing relapse or recurrence. | Conclusion is possibly out of date and this portion of the CER may need updating to include evidence for duloxetine.  | Fair. No duloxetine evidence ended up being included in this key question. |
| Key Question 2b. - For adults receiving antidepressant treatment for a depressive syndrome that either has not responded (acute phase) or has relapsed (continuation phase) or recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness? | Key Question 2b. - For adults with a depressive syndrome that has not responded to acute antidepressant treatment or has relapsed (continuation phase) or recurred (maintenance phase), do alternative second-generation antidepressants differ in their efficacy or effectiveness? |   |   |
| One head-to-head efficacy study and two effectiveness studies provide conflicting evidence on differences among second-generation antidepressants in treatment-resistant depression. The efficacy study suggests that venlafaxine is modestly more effective than paroxetine. A good-quality effectiveness study suggests that no substantial differences exist among bupropion SR, sertraline, and venlafaxine XR, but a fair-quality effectiveness study suggests that venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline.  | Results from four trials suggest no differences or only modest differences between SSRIs and venlafaxine. Numerical trends favored venlafaxine over comparator drugs in three of these trials, but differences were statistically significant in only one trial, which compared venlafaxine with paroxetine. Results from two effectiveness studies are conflicting. Based on one trial rated good, no significant differences in effectiveness exist among bupropion SR, sertraline, and venlafaxine XR. One effectiveness trial found venlafaxine to be modestly superior to citalopram, fluoxetine, mirtazapine, paroxetine, and sertraline. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Key Question 3a. - Do medications differ in their efficacy and effectiveness in treating the depressive episode? | Key Question 3 - In depressed patients with accompanying symptoms such as anxiety, insomnia, and neurovegetative symptoms, do medications or combinations of medications (including a tricyclic in combination with a second-generation antidepressant) differ in their efficacy or effectiveness for treating the depressive episode or for treating an accompanying symptoms? |   |   |
| Antidepressant medications do not differ substantially in antidepressive efficacy for patients with MDD and anxiety symptoms. | Results from five head-to-head trials suggest that efficacy does not differ substantially for treatment of depression in patients with accompanying anxiety. Results from eight head-to-head trials and three placebo-controlled trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying anxiety symptoms. Results from one head-to-head study are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting insomnia. Results from five head-to-head trials suggest that no substantial differences in efficacy exist among second-generation antidepressants for treatment of accompanying insomnia. Results are limited by study design; differences in outcomes are of unknown clinical significance. Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating depression in patients with coexisting low energy. Results from head-to-head trials are not available. Results from one placebo-controlled trial of bupropion XL are insufficient to draw conclusions about treating low energy in depressed patients. Results from head-to-head trials are not available. Results from two head-to-head trials are insufficient to draw conclusions about treating depression in patients with coexisting melancholia. Results are inconsistent across studies.  | Conclusion is still valid and this portion of the CER does not need updating. | Good |
|   | Results from two placebo-controlled trials are conflicting regarding the superiority of duloxetine over placebo. Results from head-to-head trials are not available. Evidence from one systematic review, two head-to-head trials (one poor) and five placebo-controlled trials indicate no difference in efficacy between paroxetine and duloxetine. Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating depression in patients with coexisting psychomotor change. Results from one head-to-head trial are insufficient to draw conclusions about the comparative efficacy for treating somatization in depressed patients. Results indicate similar improvement in somatization. Evidence from one open-label head-to-head trial is insufficient to draw conclusions about the comparative efficacy for treating coexisting somatization in depressed patients. Results indicate no difference in effectiveness. |   | Not applicable. This is a new conclusion not present in the original report, but is consistent with the overall "no difference in drugs" conclusion from the original report and thus would not change clinical practice. |
| Key Question 3b. - Do medications differ in their efficacy and effectiveness in treating the accompanying symptoms? | No Key Question 3b. |   |   |
| One fair-quality head-to-head trial reported no statistically significant difference between fluoxetine and sertraline for treating depression in patients with psychomotor retardation. The same study found that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation. | One fair-quality head-to-head trial reported no statistically significant difference between fluoxetine and sertraline for treating depression in patients with psychomotor retardation. The same study found that sertraline was more efficacious than fluoxetine for treating depression in patients with psychomotor agitation.  | Conclusion is possibly out of date and this portion of the CER may need to be updated to add points regarding treatment of Parkinson’s symptoms and pain (see below).  | Fair. The Parkinson's symptom data ended up not being included in the updated CER.  |
| Key Question 4 - For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more severe events including suicide. | Key Question 4a. - For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea, diarrhea, headache, tremor, daytime sedation, decreased libido, failure to achieve orgasm, nervousness, insomnia, and more serious events including suicide. |   |   |
| Constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence were commonly and consistently reported adverse events. On average, 61 percent of patients in efficacy trials experienced at least one adverse event. Nausea and vomiting were found to be the most common reasons for discontinuation in efficacy studies. Overall, second-generation antidepressants have similar adverse events profiles. | Adverse events profiles, based on 92 efficacy trials and 48 studies of experimental or observational design, are similar among second generation antidepressants. The incidence of specific adverse events differs across antidepressants. Meta-analysis of 15 studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class. Results from seven trials indicate that mirtazapine leads to higher weight gains than citalopram, fluoxetine, paroxetine, and sertraline. Results from 15 studies indicate that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine. Results from one systematic review confirm some of these findings. Results from six trials indicate that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine. | Conclusion is still valid and this portion of the CER does not need updating. | Good |
| Discontinuation syndromes (e.g., headache, dizziness, nausea) occurred in 0 to 86 percent of patients. Paroxetine and venlafaxine had the highest incidence of this problem, and fluoxetine the lowest incidence.  | A good systematic review indicates that paroxetine and venlafaxine have the highest rates of discontinuation syndrome; fluoxetine has the lowest. | Conclusion is possibly out of date and this portion may need updating. New analyses should be reviewed for methods, inclusion criteria, funding source.  | Fair. Whatever new evidence was added did not change the conclusions |
| Overall discontinuation rates did not differ significantly between SSRIs as a class and bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. In the case of venlafaxine compared with SSRIs, higher discontinuation rates because of adverse events appear to be balanced by lower discontinuation rates because of lack of efficacy. | Meta-analyses of numerous efficacy trials indicate that overall discontinuation rates are similar. Duloxetine and venlafaxine have a higher rate of discontinuations because of adverse events than SSRIs as a class. Venlafaxine has a lower rate of discontinuations because of lack of efficacy than SSRIs as a class. | Conclusion is possibly out of date and this portion may need updating based on new analysis showing lower drop out rate with escitalopram.  | Fair. The escalitopram data did not end up in the conclusions. |
| Bupropion is associated with a lower incidence of sexual dysfunction than fluoxetine, paroxetine, and sertraline. In head-to-head trials, paroxetine consistently had higher rates of sexual dysfunction than comparators (fluoxetine, fluvoxamine, nefazodone, and sertraline). | Results from six trials indicate that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline. Among SSRIs, paroxetine has the highest rates of sexual dysfunction. | Conclusion is still valid and this portion of the CER does not need updating. | Good. |
| The existing evidence on the comparative risk for rare but severe adverse events, such as suicidality, seizures, cardiovascular events (i.e., elevated systolic and diastolic blood pressure and elevated pulse/heart rate), hyponatremia, hepatotoxicity, and serotonin syndrome, is insufficient to draw firm conclusions.  | No trials or observational studies assessing hyponatremia met criteria for inclusion in this review. One cohort study not meeting inclusion criteria suggested that hyponatremia was more common in elderly patients treated with various antidepressants than in placebo-treated patients. Evidence from existing studies is insufficient to draw conclusions about the comparative risk of hepatotoxicity. Weak evidence indicates that nefazodone might have an increased risk of hepatotoxicity. No trials or observational studies assessing serotonin syndrome were included in this review. Numerous case reports of this syndrome exist but were not included in this review.  | Conclusion is possibly out of date and this portion of the CER may need updating based on new U.K. cohort study of over 200,000 patients. | Fair. The study identified by surveillance assessment, Rubino, A., N. Roskell, et al. (2007). "Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study." BMJ 334(7587): 242 was not included in the updated CER. However, it seems to meet inclusion criteria of being an observational study of an adverse event with a sample size of greater than 1,000.  |
|   | Results from 11 observational studies (two good quality), five metaanalyses or systematic reviews (four good), and one systematic review yield conflicting information about the comparative risk of suicidality. Results from three studies (one good observational design) yield conflicting information about the comparative risk of seizures. Results from one good observational study and one pooled analysis yield noncomparative or conflicting information about the comparative risk of cardiovascular events. Evidence from existing studies is insufficient to draw conclusions about adherence in real-world settings. |   | This is a new conclusion, but consistent with the overall "no difference in drugs" and not one that will change clinical practice. |
| No Key Question 4b. | Key Question 4b. - Are there any differences in safety, adverse events, or adherence between immediate release and extended-release formulations of second-generation antidepressants? |   |   |
|   | Findings from one trial each indicate that no differences in harms exist between fluoxetine daily and fluoxetine weekly or between venlafaxine IR and venlafaxine XR. One trial provides evidence that paroxetine IR leads to higher rates of nausea than paroxetine CR. One trial provides evidence that fluoxetine weekly has better adherence rates than fluoxetine daily. Evidence from one observational study indicates that prescription refills are more common with the extended-release than the immediate-release formulation of bupropion. |   | This is a new conclusion, but consistent with the overall "no difference in drugs" and not one that will change clinical practice. |
| Key Question 5 - How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations:\* Elderly or very elderly patients; \*Other demographic groups (defined by age, ethnic or racial groups, and sex);\* Patients with medical comorbidities (e.g., ischemic heart disease, cancer)? | Key Question 5 - How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations? o Elderly or very elderly patientso Other demographic groups (defined by age, ethnic or racial groups, and sex)o Patients with medical comorbidities (e.g., ischemic heart disease, cancer)o Patients with psychiatric and behavioral comorbidities (e.g., substance abuse disorders)o Patients taking other medications |   |   |
| No major differences in efficacy and effectiveness exist among second-generation antidepressants in elderly or very elderly populations. Indirect evidence suggests that efficacy among second-generation antidepressants does not differ between men and women. | Evidence from 11 trials indicates that efficacy does not differ substantially among second-generation antidepressants for treating MDD in patients age 60 years or older. No head-to-head evidence found for dysthymia or subsyndromal depression. Results from one good placebo-controlled trial showed no difference between fluoxetine and placebo. No evidence in older patients with MDD. One effectiveness study showed greater improvement with paroxetine versus placebo in dysthymia patients older than 60 years; insufficient evidence to draw conclusions on comparative effectiveness. Results from six studies indicate that adverse events may differ somewhat across second-generation antidepressants in older adults. No head-to-head studies were found for dysthymia or subsyndromal depression. Two trials suggest differences between men and women in sexual side effects. Results from a subgroup analysis of one trial indicate significantly greater response with venlafaxine XR than fluoxetine in patients with MDD and comorbid generalized anxiety disorder. Placebo-controlled trials assessed efficacy in patients with the following comorbidities: alcohol/substance abuse, Alzheimer’s disease/dementia, arthritis, diabetes, HIV/AIDS, multiple sclerosis, stroke, and vascular disease. No head-to-head evidence exists on comparative efficacy.  | Conclusion should be updated to include new data on racial/ethnic populations.  | Fair. There were no changes to the conclusions or SOE for race or ethnicity subpopulations.  |

**References**

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