

Drug Class Review

Second-generation Antidepressants

Levomilnacipran, Vilazodone, and Vortioxetine Compared with Other Second-generation Antidepressants

Targeted Update Final Report

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Published in a separate document.

INTRODUCTION

Major depressive disorder (MDD),¹ defined as the presence of depressed mood or loss of interest or pleasure, along with at least 4 additional MDD diagnosis criteria or symptoms for at least 2 weeks, is the most prevalent and disabling form of depression, affecting more than 16 percent of US adults (lifetime).² MDD can be characterized as mild, moderate, or severe based on symptom severity, functional impairment, and level of patient distress.¹ MDD also exerts a negative impact on physical health. It reduces participation in preventive health care activities^{3,4} and adherence to medical treatment.⁵ It increases the likelihood of chronic conditions such as obesity, smoking, sedentary lifestyles, and hypertension^{6,7} as well as amplifies the risk of cancer⁸ and death following myocardial infarction.⁶ Mortality rates attributable to MDD and other depressive illnesses are high; approximately 4 percent of adults with a mood disorder commit suicide, and depression precedes about two-thirds of deaths due to suicide.⁹

Generalized anxiety disorder (GAD) is defined as excessive anxiety and worry about a variety of topics, events, or activities for at least 6 months.¹ GAD is accompanied by a variety of physical symptoms, such as fatigue, fidgeting, headache, muscle tension, muscle aches, and others. GAD affects approximately 5.7% of adults in the US over a lifetime.¹⁰ GAD affects women twice as much as men and is the most common cause for workplace disability in the US.¹¹

Second-generation antidepressants dominate the medical management of MDD and GAD. They include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and drugs that affect other neurotransmitters. The mechanism of action of most second-generation antidepressants, however, is only poorly understood. In general, these drugs work through their effect on prominent neurotransmitters in the central nervous system. The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, vortioxetine) act by selectively inhibiting the reuptake of serotonin (5-hydroxy-tryptamine, 5-HT) at the presynaptic neuronal membrane. Vilazodone also acts as a 5-HT_{1A} agonist; vortioxetine is also a 5-HT_{1A} agonist but has also antagonistic effects on several 5-HT receptors (5-HT₃, 5-HT_{1D}, and 5-HT₇).

The SNRIs (duloxetine, desvenlafaxine, levomilnacipran, venlafaxine) are potent inhibitors of serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Mirtazapine, sometimes characterized as an SNRI, is believed to enhance central noradrenergic and serotonergic activity as a 5-HT₂ and 5-HT₃ receptor antagonist. Nefazodone is believed to inhibit neuronal uptake of serotonin and norepinephrine. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine.

With the exception of fluvoxamine, which is approved only for the treatment of obsessive-compulsive disorder (OCD), all of the second-generation antidepressants are approved for the treatment of MDD. Currently, only duloxetine, escitalopram, paroxetine, and venlafaxine are approved for the treatment of GAD. Table 1 presents standard dosing for second-generation antidepressants that are available in the United States.

Table 1: Second-generation antidepressant: Approved total daily dosing range and frequency of administration for adults

Generic Name	U.S. Trade Name ^a	Usual Daily Dosing Range	Frequency
Bupropion	Wellbutrin®	200–450 mg	Three times daily
	Wellbutrin SR®	150–400 mg	Twice daily
	Wellbutrin XL®	150–450 mg	Once daily
Citalopram	Celexa®	20–40 mg	Once daily
Desvenlafaxine	Pristiq®	50 mg	Once daily
Duloxetine	Cymbalta®	40–60 mg	Once or twice daily
Escitalopram	Lexapro®	10–20 mg	Once daily
Fluoxetine	Prozac®	10–80 mg	Once or twice daily
	Prozac Weekly®	90 mg	Once weekly
Fluvoxamine	Luvox®	50–300 mg	Once or twice daily
Levomilnacipran	Fetzima®	40–120 mg	Once daily
Mirtazapine	Remeron®	15–45 mg	Once daily
	Remeron Sol tab®	15–45 mg	Once daily
Nefazodone	Serzone®	200–600 mg	Twice daily
Paroxetine	Paxil®	20–60 mg	Once daily
	Paxil CR®	12.5–75 mg	Once daily
Sertraline	Zoloft®	50–200 mg	Once daily
Trazodone	Desyrel®	150–400 mg	Three times daily
Venlafaxine	Effexor®	75–375 mg	Two to three times daily
	Effexor XR®	75–225 mg	Once daily
Vilazodone	Viibryd®	40 mg	Once daily
Vortioxetine	Trintellix®	10–20 mg	Once daily

Abbreviations: ^a CR, SR, XL, and XR are registered trademarks referring to controlled-, sustained-, or extended-release dosage forms, respectively; mg, milligram;

Scope and Key Questions

The purpose of this targeted review is to help policymakers and clinicians make informed choices about the use of second-generation antidepressants. Our goal is to summarize comparative data on the efficacy, effectiveness, tolerability, and safety of levomilnacipran, vilazodone, and vortioxetine compared with one another and with other second-generation antidepressants.

The participating organizations approved the following key questions to guide this review:

1. For outpatients with major depressive disorder or generalized anxiety disorder: do levomilnacipran, vilazodone, or vortioxetine differ in efficacy or effectiveness compared with other second-generation antidepressants?
2. For outpatients with major depressive disorder or generalized anxiety disorder: do levomilnacipran, vilazodone, or vortioxetine differ in harms compared with other second-generation antidepressants?
3. Are there subgroups of patients based on demographics (age, racial groups, socio-demographic factors, and sex), other medications, or comorbidities for which one drug (levomilnacipran, vilazodone, or vortioxetine) is more effective or associated with fewer adverse events than another?

Inclusion Criteria

Populations

Adult outpatient populations with major depressive disorder or generalized anxiety disorder (as diagnosed by a validated instrument).

Interventions

Levomilnacipran, vilazodone, vortioxetine

Comparators

All second-generation antidepressants as listed in Table 1

Efficacy or Effectiveness Outcomes

- Response
- Remission
- Time to onset of efficacy
- Prevention of relapse and recurrence
- Quality of life
- Functional capacity
- Hospitalization

Harms Outcomes

- Overall risk of adverse events
- Overall discontinuation of treatment
- Discontinuation because of adverse events
- Serious adverse events, including
 - Hyponatremia
 - Hepatotoxicity
 - Serotonin syndrome
 - Suicidal ideas or behaviors
 - Others
- Specific adverse events, including:
 - Gastrointestinal symptoms
 - Nausea and vomiting
 - Sexual dysfunction
 - Weight gain
 - Others

Study Designs

For efficacy and effectiveness, we included double-blinded, randomized controlled trials (RCTs) comparing levomilnacipran, vilazodone, or vortioxetine with one another or with another second-generation antidepressant. In addition, for harms, non-randomized controlled studies with a sample size of 100 participants or more were eligible. Because we conducted network meta-analyses, we also included any double-blinded RCT comparing second-generation antidepressants with one another or with placebo. All eligible studies had a minimum treatment duration of 6 weeks.

METHODS SUMMARY

We followed the methods for systematic reviews outlined in the DERP Methods Manual, including for example, dual review of all decisions. See

<http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm>. A summary of key points is provided below.

Literature Search

We searched multiple electronic databases through the third week of September 2016 (see Appendix B for complete search strategies).

Validity Assessment

For RCTs, we assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.¹² Trials were rated as good, fair or poor according to these criteria and methods.

Grading the Strength of Evidence

We graded the strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.¹³ Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Table 2 describes the grades of strength of evidence that can be assigned.

We graded the strength of evidence for response, remission, quality of life, functional capacity, serious adverse events, overall risk for adverse events, discontinuation because of adverse events, and suicidal ideas and behavior. We chose these outcomes because key informants and a technical expert panel of a recent comparative effectiveness review on treatment options for MDD anonymously ranked them in a web-based survey as critical or important for decision-making.¹⁴

Table 2: Strength of evidence grades and definitions¹³

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Data Synthesis (see Appendix E for detailed methods)

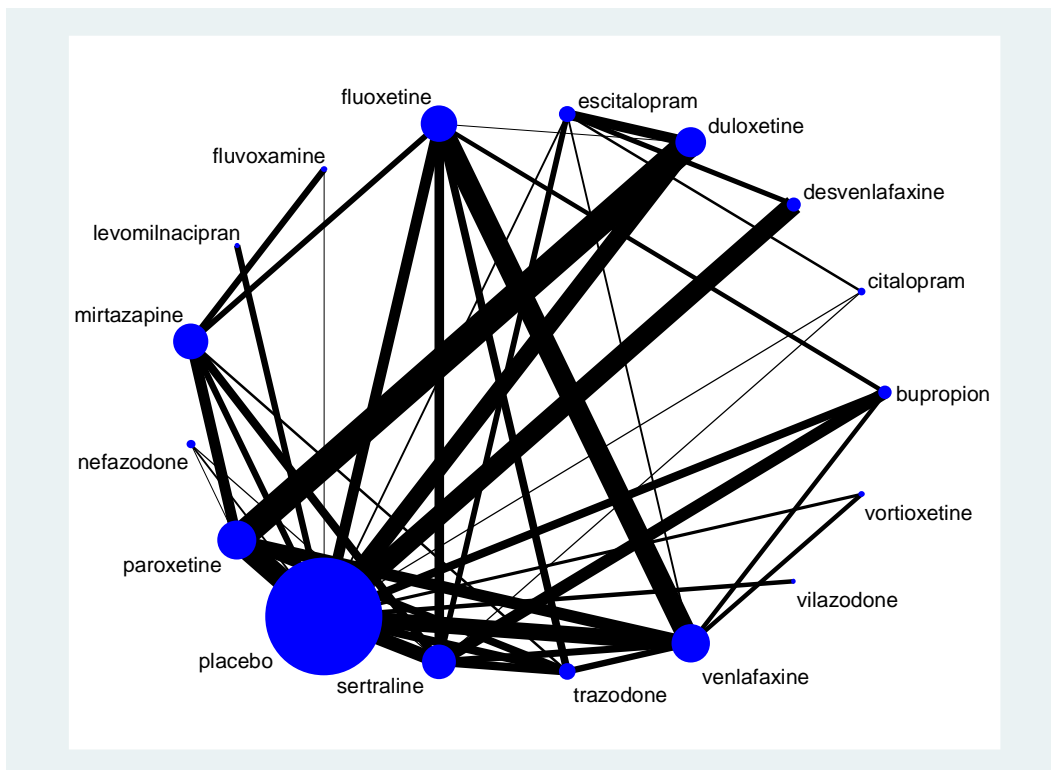
We conducted meta-analyses of outcomes of interest if a sufficient number of studies were homogeneous enough that combining their results could be justified. For all meta-analyses we used random- and fixed-effects models. For random-effects models, we employed restricted maximum likelihood methods. For fixed-effects models, we used the Mantel-Haenszel method. We conducted all pairwise meta-analyses with OpenMetaAnalyst (www.cebm.brown.edu/openmeta). To assess statistical heterogeneity between studies, we

calculated the Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity).¹⁵

Network meta-analyses

Because we were aware of the dearth of studies directly comparing some interventions of interest, we planned a priori with prespecified criteria to conduct network meta-analyses on response to treatment with a random-effects multivariate approach using restricted maximum likelihood methods. To conduct network meta-analyses, we included all placebo- and active-controlled RCTs that were homogenous in study populations and outcome assessments and were part of a connected network. We built on a database of relevant RCTs of a previous report on the comparative efficacy and safety of second-generation antidepressants for the treatment of MDD.¹⁴ Our outcome measure of choice was response to treatment on the Hamilton Depression Rating Scale (defined as a 50 percent improvement of scores from baseline). Figure 1 presents the network of 119 RCTs that we used for network meta-analysis.

Figure 1: Display of the network of comparisons used for network meta-analyses

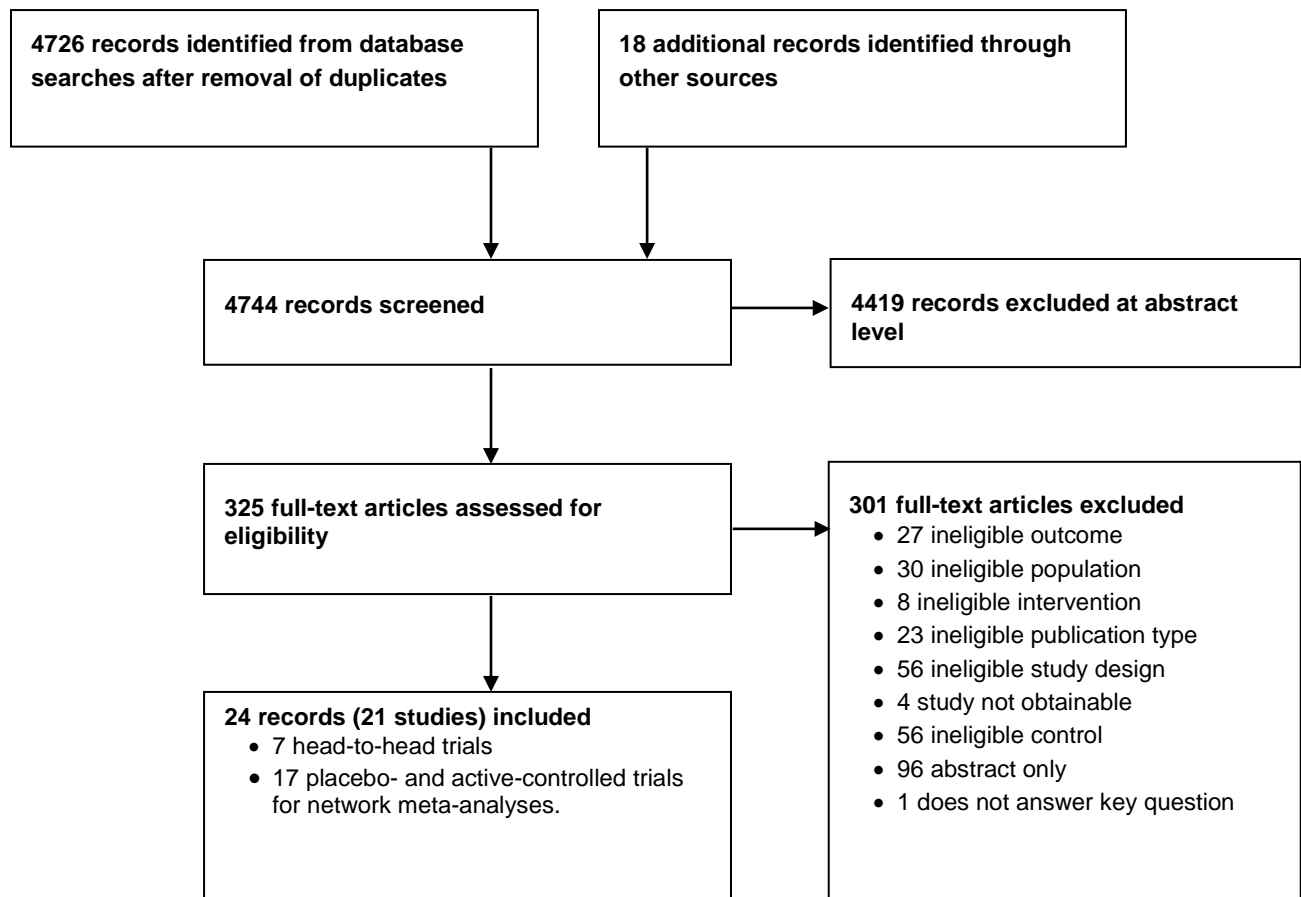


RESULTS

Overview

Literature searches identified 4,744 citations. We received dossiers from 1 pharmaceutical manufacturer, Takeda Pharmaceuticals U.S.A., Inc. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 325 citations. After reapplying the criteria for inclusion, we ultimately included 24 publications, representing 7 unique head-to-head studies and 14 placebo- and active-controlled trials. See Appendix C for a list of excluded studies and reasons for exclusion at this stage. Figure 2 shows the flow of study selection.

Figure 2: Results of literature search^a



^a The Drug Effectiveness Review Project uses a modified PRISMA flow diagram.¹⁶

Summary of Findings

Key Question 1

- We did not find eligible studies for most direct comparisons of levomilnacipran, vilazodone, or vortioxetine with one another or with other second-generation antidepressants for the treatment of MDD or GAD.
- For all comparisons, no eligible evidence was available on quality of life, hospitalizations, time to onset of efficacy, and prevention of relapse and recurrence.
- Results of network meta-analyses, overall, rendered similar response rates between levomilnacipran, vilazodone, or vortioxetine and other second-generation antidepressants (network meta-analysis, low or insufficient strength of evidence).
- One trial reported similar response rates for vilazodone and citalopram for the treatment of patients with MDD (1 RCT, moderate strength of evidence).
- Results of two trials comparing directly vortioxetine and duloxetine for the treatment of MDD were conflicting on response to treatment. Network meta-analysis indicated similar response rates (2 RCTs, network meta-analysis, low strength of evidence). Remission rates were similar after 8 weeks of treatment (2 RCTs, moderate strength of evidence). Improvements in functional capacity were also similar. (1 RCT, low strength of evidence).
- Vortioxetine and venlafaxine XR led to similar response and remission rates after 6 weeks of treatment in patients with severe MDD (1 RCT and network meta-analysis [response only], moderate strength of evidence).
- Based on a single trial, vortioxetine led to numerically lower response and remission rates than duloxetine after 8 weeks of treatment for GAD. Differences in treatment effects, however, did not reach statistical significance (1 RCT, low strength of evidence).

Key Question 2

- Three trials reported data on harms comparing vortioxetine with duloxetine; one trial compared vortioxetine with venlafaxine XR. Three studies included patients with MDD; one study, patients with GAD.
- We did not find any eligible trials comparing levomilnacipran with other second-generation antidepressants.
- Vilazodone and citalopram had similar risks of overall adverse events (1 RCT, moderate strength of evidence) and overall discontinuation (1 RCT, strength of evidence not rated) after 10 weeks of treatment.
- Significantly more patients treated with vilazodone experienced diarrhea and vomiting than patients treated with citalopram (1 RCT, strength of evidence not rated).
- Vortioxetine led to similar risks of overall adverse events as duloxetine (3 RCTs, high strength of evidence) and venlafaxine XR (1 RCT, moderate strength of evidence) after 8 and 6 weeks of treatment, respectively.
- Overall discontinuation rates were similar between vortioxetine and duloxetine (3 RCTs, strength of evidence not rated), and vortioxetine and venlafaxine XR (1 RCT, strength of evidence not rated).

- Rates of discontinuation because of adverse events were similar between patients on vortioxetine and duloxetine (3 RCTs, low strength of evidence) but numerically lower in patients treated with vortioxetine than venlafaxine XR (1 RCT, low strength of evidence).
- Risks for most specific adverse events (e.g., constipation, diarrhea, nausea, vomiting) were statistically not significantly different between patients treated with vortioxetine or duloxetine (2 or 3 RCTs, depending on adverse event; strength of evidence not rated). Likewise, risks for specific adverse events were similar between vortioxetine and venlafaxine XR (1 RCT, strength of evidence not rated).
- Vortioxetine led to statistically significantly lower rates of sexual dysfunction (2 RCT) and somnolence (1 RCT) than duloxetine (strength of evidence not rated).
- Serious adverse events were rare and statistically not significantly different between vortioxetine and duloxetine (3 RCTs, low strength of evidence) or venlafaxine XR (1 RCT, low strength of evidence).

Key Question 3

- We did not find any eligible evidence to address this key question.

The following sections are organized by key question. We first present results on MDD and then results on GAD. Table 2 provides details on strength of evidence ratings for main outcomes.

Key Question 1. For outpatients with major depressive disorder (MDD) or generalized anxiety disorder (GAD): do levomilnacipran, vilazodone, or vortioxetine differ in efficacy or effectiveness compared with one another or other second-generation antidepressants?

Detailed Assessment: Major Depressive Disorder

Our searches found 5 eligible RCTs that directly compared vortioxetine with other second-generation antidepressants.¹⁷⁻²¹ We did not find any studies directly comparing levomilnacipran or vilazodone with other second-generation antidepressants.

Two of the vortioxetine trials used doses that were outside the approved dosing range (2.5mg and 5mg per day; the approved dosing range is 10mg to 20mg per day).^{17,18} Because of concerns about a lack of dosing equivalence with the active comparator duloxetine, we did not include these studies in our analyses. The remaining 3 RCTs compared vortioxetine with duloxetine^{20,21} and venlafaxine XR (extended release).¹⁹ Table 3 summarizes study characteristics and results. More detailed data abstraction can be found in the accompanying evidence tables.

Table 3: Study characteristics and results of eligible trials comparing vortioxetine with other second-generation antidepressants

Authors, Year	Study design, comparisons, dosage (mg), duration	Population (N)	Primary outcome, secondary outcomes	Efficacy Results	Quality rating
VILAZODONE compared with CITALOPRAM					
Mathews et al., 2015 ²²	RCT Vilazodone 20* Vilazodone 40 Citalopram 40 Placebo 10 weeks	Outpatients with primary, acute phase MDD (1162)	Change on MADRS Response on MADRS, CGI-S scores, CGI-I scores, C-SSRS assessment, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Similar response rates between vilazodone and citalopram	Fair
VORTIOXETINE compared with DULOXETINE					
Katona et al., 2012 ¹⁷	RCT Vortioxetine 5* Duloxetine 60 Placebo 8 weeks	Outpatients over 65 years with primary, acute phase MDD (453)	Change on HAM-D ₂₄ Change on MADRS, CGI-S scores, CGI-I scores, response, remission, improvement of cognition, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Vortioxetine outside approved dosing range, results not reported.	Good
Mahableshwarkar et al., 2013 ¹⁸	RCT Vortioxetine 2.5* Vortioxetine 5* Duloxetine 60 Placebo 8 weeks	Outpatients with primary, acute phase MDD (611)	Change on HAM-D ₂₄ Response, remission on MADRS, change on CGI-I, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Vortioxetine outside approved dosing range, results not reported.	Fair
Mahableshwarkar et al., 2015 ²⁰	RCT Vortioxetine 15 Vortioxetine 20 Duloxetine 60 Placebo 8 weeks	Outpatients with primary, acute phase MDD (614)	Change on MADRS Response, remission, change on CGI-I, change on SDS, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Higher response rates for duloxetine than vortioxetine Similar remission rates between vortioxetine and duloxetine.	Fair
Mahableshwarkar, et al., 2015 ²¹	RCT Vortioxetine 10-20 Duloxetine 60 Placebo 8 weeks	Outpatients with primary, acute phase MDD (602)	Change on DSST performance score Response, remission, change on CGI-I, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Similar response and remission rates between vortioxetine and duloxetine.	Fair

Table 4 (continued): Study characteristics and results of eligible trials comparing vortioxetine with other second-generation antidepressants

Authors, Year	Study design, comparisons, dosage (mg), duration	Population (N)	Primary outcome, secondary outcomes	Efficacy Results	Quality rating
VORTIOXETINE compared with VENLAFAXINE XR					
Alvarez et al., 2012 ¹⁹	RCT Vortioxetine 5* Vortioxetine 10 Venlafaxine XR 225 Placebo 6 weeks	Outpatients with primary, acute phase MDD (429)	Change on HAM-D ₂₄ Response, remission on MADRS, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Similar response and remission rates between vortioxetine and venlafaxine XR	Fair

* Outside approved dosing range, results not reported

Abbreviations: CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; C-SSRS, Columbia-Suicide Severity Rating Scale; DSST, digit symbol substitution test; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; mg, milligram; N, number of patient included; RCT, randomized controlled trial; SDS, Sheehan Disability Scale; XR, extended release

Levomilnacipran compared with other second-generation antidepressants

Our searches did not find any eligible studies that directly compared levomilnacipran with other second-generation antidepressants for the treatment of MDD. Network meta-analyses indicate no statistically significant differences in response rates between levomilnacipran and other second-generation antidepressants (see Figure 3). Sensitivity analyses including high risk of bias studies yielded consistent estimates. Figure 3 provides more details about underlying assumptions and sensitivity analyses of network meta-analyses.

Vilazodone compared with citalopram

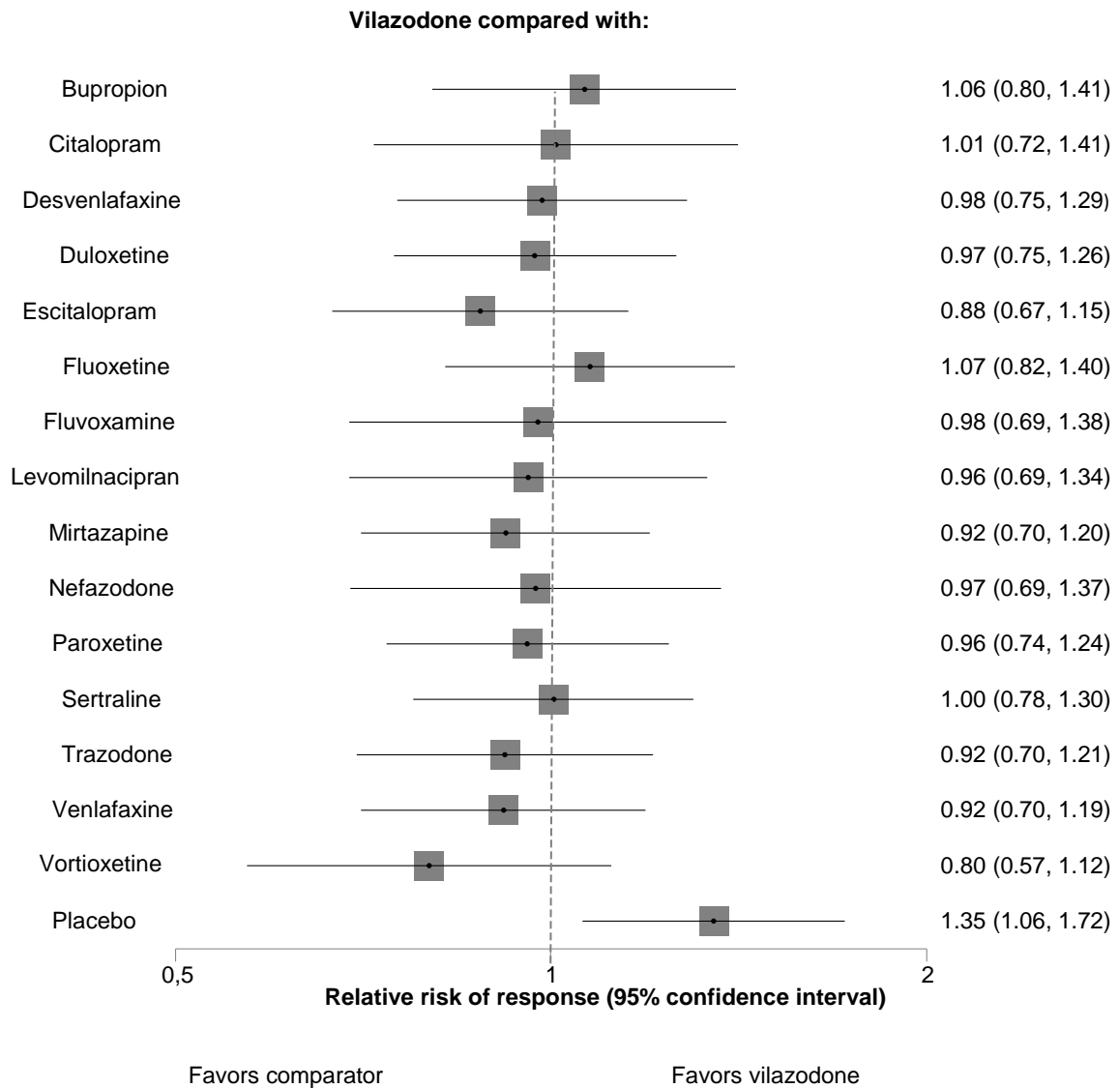
A fair-quality, double-blinded, multicenter RCT compared vilazodone (20mg and 40 mg per day) with citalopram (40mg per day) during 10 weeks of treatment.²² The study was funded by the producer of vilazodone. Because vilazodone 20mg per day is outside the approved dosing range, we do not report results of this treatment arm. A total of 580 patients were randomized to vilazodone 40mg per day or citalopram.

The primary efficacy outcome was the change on the Montgomery Asberg Depression Rating Scale from baseline to week 10. Patients in the vilazodone 40mg and the citalopram arms experienced similar reductions of scores after 10 weeks (-17.6 vs. -17.5 points). Response rates (64.6% vs. 62.9%; RR 1.03, 95% CI 0.90 to 1.16 [self-calculated]) were also similar between the 2 treatment groups. The publication did not report on remission or other outcomes of interest. Results from network meta-analyses provided similar results for response (RR 1.01, 95% CI 0.72 to 1.41; see Figure 4).

Vilazodone compared with other second-generation antidepressants

Except for the RCT comparing vilazodone with citalopram, our searches did not find any eligible studies that directly compared vilazodone with other second-generation antidepressants for the treatment of MDD. Network meta-analyses indicate no statistically significant differences in response rates between vilazodone and other second-generation antidepressants (see Figure 4). Sensitivity analyses including high risk of bias studies yielded consistent estimates. Appendix E provides more details about underlying assumptions and sensitivity analyses of network meta-analyses.

Figure 4: Results of network meta-analyses for response to treatment comparing vilazodone with other second-generation antidepressants



Vortioxetine compared with duloxetine

Two fair-quality, double-blinded, multicenter RCTs compared vortioxetine with duloxetine during 8 weeks of treatment.^{20,21} Both studies were funded by the producer of vortioxetine. One trial was a phase III fixed-dose RCT randomizing 614 outpatients with MDD to vortioxetine 15mg, vortioxetine 20mg, duloxetine 60mg, or placebo.²⁰ The primary outcome was the mean change on the Montgomery Asberg Depression Rating Scale from baseline to week 8. The second trial assessed the impact of flexible-dose vortioxetine (10-20mg per day), fixed-dose duloxetine (60mg per day), or placebo on cognitive functioning as the primary outcome in 602 patients with MDD.²¹

In the phase III trial, statistically significantly fewer patients in the vortioxetine 15mg and 20mg groups achieved response to treatment at 8 weeks than patients on duloxetine (44.1% vs. 44.2% vs. 54.8%; RR 0.81, 95% CI 0.67 to 0.98 [self-calculated, combining both vortioxetine arms]).²⁰ By contrast, response rates in the trial using a flexible dose of vortioxetine were similar between patients in the vortioxetine and the duloxetine groups (50.9% vs. 54.5%; RR 0.98, 95% CI 0.92 to 1.19 [self-calculated]).^{21,23} Results from network meta-analyses indicated similar response rates between vortioxetine and duloxetine (RR 1.22, 95% CI 0.95 to 1.56; see Figure 5).

Both studies reported similar remission rates (Montgomery Asberg Depression Rating Scale total score ≤ 10) at 8 weeks. For example, in the trial using flexible-dose vortioxetine, 30.3% of patients treated with vortioxetine achieved remission compared with 33.7% on duloxetine (RR 0.90, 95% CI 0.67 to 1.19 [self-calculated]).^{21,23}

Changes on the Sheehan Disability Scale were also similar among patients in the vortioxetine and the duloxetine groups. None of the 3 active treatments, however, yielded improvements that were statistically significantly greater than those in the placebo group.²⁰ Likewise, cognitive functioning was similar between patients treated with vortioxetine or duloxetine.²¹

Vortioxetine compared with venlafaxine XR

The only study that addressed this comparison was a phase II fixed-dose clinical trial that compared 2 doses of vortioxetine (5mg and 10mg per day) with venlafaxine XR (225mg per day), and placebo.¹⁹ Because 5mg per day are below the approved dosing range of vortioxetine (i.e., 10mg to 20mg per day), we do not report results of this treatment arm.

This fair-quality, double-blinded trial enrolled 429 outpatients (n=320 without the vortioxetine 5mg arm) with severe MDD from Australia, Europe, and Malaysia. The study was funded by the producer of vortioxetine.

The primary efficacy outcome was the change on the Montgomery Asberg Depression Rating Scale from baseline to week 6. Patients in the vortioxetine 10mg and the venlafaxine XR arms experienced similar reductions of scores after 6 weeks (-22.9 vs. -23.4 points). Response (69.0% vs. 72.0%; RR 0.98, 95% CI 0.82 to 1.16 [self-calculated]) and remission rates (45.0% vs. 46.0%; RR 0.98, 95% CI 0.73 to 1.31 [self-calculated]) on the Hamilton Depression Rating Scale were also similar between the 2 treatment groups.

Results from network meta-analyses provided similar results for response (RR 1.15, 95% CI 0.91 to 1.45; see Figure 5).

Vortioxetine compared with other second-generation antidepressants

Our searches did not find any eligible studies that directly compared vortioxetine with second-generation antidepressants other than duloxetine and venlafaxine XR for the treatment of MDD. Network meta-analyses indicate no statistically significant differences in response rates between vortioxetine and second-generation antidepressants for most comparisons (see Figure 5).

Exceptions are the comparisons with bupropion and fluoxetine for which vortioxetine yielded statistically significantly higher response rates than comparators (RR 1.33, 95% CI 1.02 to 1.74 compared with bupropion; RR 1.35, 95% CI 1.05 to 1.73 compared with fluoxetine).

To explore the robustness of these results, we conducted sensitivity analyses. When we added high risk of bias studies to the network meta-analysis model, the comparison with bupropion lost statistical significance (RR 1.29, 95% CI 0.99 to 1.68). The difference in response

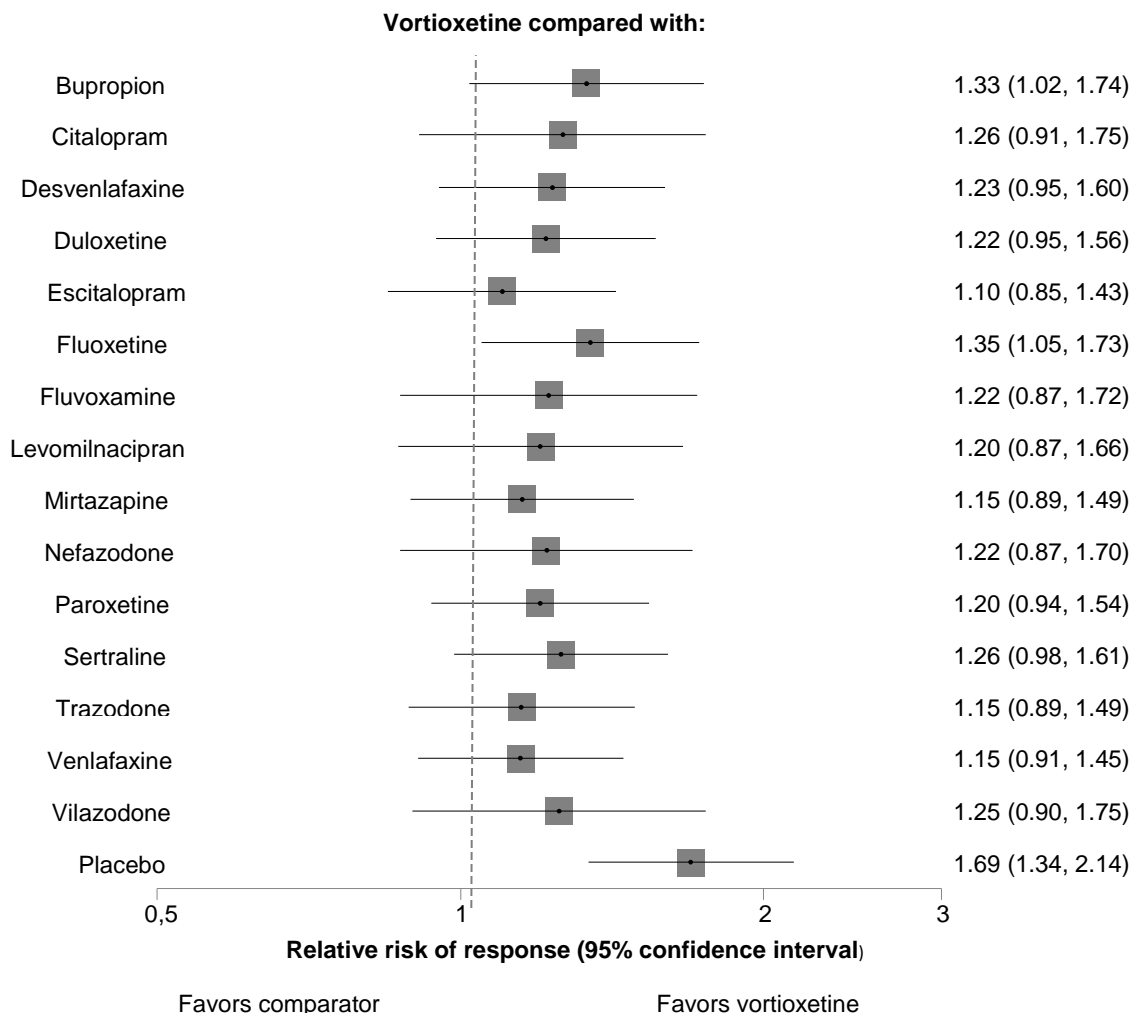
rates for the comparison of vortioxetine with fluoxetine, however, remained statistically significant (RR 1.30, 95% CI 1.02 to 1.67).

When we explored the contribution of individual vortioxetine studies to the overall results of the network meta-analysis, it turned out that effect estimates were strongly determined by a single study (Henigsberg et al.)²⁴, which reported substantially higher response rates for patients on vortioxetine than on placebo (RR 2.16, 95% CI 1.52 to 3.05). Removing the Henigsberg et al. study from the model led to non-statistically significant response rates between vortioxetine and bupropion (RR 1.20, 95% CI 0.89 to 1.63), and vortioxetine and fluoxetine (RR 1.22, 95% CI 0.91 to 1.62).

To achieve a broader evidence base for this comparison, we added response rates of vortioxetine versus placebo on the Montgomery Asberg Depression Rating Scale from 2 trials that did not report results on the Hamilton Depression Rating Scale.^{20,21} In these sensitivity analyses, response rates between vortioxetine and bupropion (RR 1.05, 95% CI 0.84 to 1.31), and vortioxetine and fluoxetine (RR 1.07, 95% CI 0.87 to 1.31) were not statistically significantly different.

Appendix E provides more details about underlying assumptions and sensitivity analyses of the network meta-analysis.

Figure 5: Results of network meta-analyses for response to treatment comparing vortioxetine with other second-generation antidepressants



Detailed Assessment: Generalized Anxiety Disorder

We did not find any studies directly comparing levomilnacipran or vilazodone with other second-generation antidepressants for the treatment of GAD. We found 1 eligible RCT that directly compared vortioxetine with duloxetine and placebo for patients with GAD.²⁵ Vortioxetine is currently not approved for the treatment of GAD. In this trial, 2 treatment arms used vortioxetine doses that were outside the approved dosing range (2.5mg and 5mg per day; the approved dosing range is 10mg to 20mg per day). Because of concerns about a lack of dosing equivalence with the active comparator duloxetine, we did not include results of these treatment arms in our analyses. Table 4 summarizes study characteristics and results. More detailed data abstraction can be found in the accompanying evidence tables.

Table 5: Study characteristics and results of the eligible trial comparing vortioxetine with duloxetine

Authors,Year	Study design, comparisons, dosage (mg), duration	Population (N)	Primary outcome, secondary outcomes	Efficacy Results	Quality rating
VORTIOXETINE compared with DULOXETINE					
Mahableshwarkar et al., 2014 ²⁵	RCT Vortioxetine 2.5* Vortioxetine 5* Vortioxetine 10 Duloxetine 60 Placebo 8 weeks	Adult patients with primary diagnosis of GAD (781)	Change on HAM-A Response, remission, change on CGI-I, change on SDS, risk of adverse events, overall discontinuation, discontinuation because of adverse events	Numerically lower response and remission rates for vortioxetine than duloxetine	Fair

* Outside approved dosing range, results not reported

Abbreviations: CGI-I, Clinical Global Impression-Improvement; GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Scale; mg, milligram; N, number of patients included; RCT, randomized controlled trial, SDS, Sheehan Disability Scale

Vortioxetine compared with duloxetine

The only study that compared the efficacy of vortioxetine for the treatment of GAD with another second-generation antidepressant was a fair-quality, phase III, multicenter, fixed-dose clinical trial that compared 3 doses of vortioxetine (2.5mg, 5mg, and 10mg per day) with duloxetine (60mg per day), and placebo.²⁵ As explained above, for the vortioxetine, we report only results of the 10mg group.

The trial involved 781 adult outpatients with a primary diagnosis of GAD who had been recruited from 72 centers in the United States. Of those, 156 patients were randomized to the vortioxetine 10mg group and 156 patients to the duloxetine 60mg group. The study was funded by the producer of vortioxetine.

The primary efficacy outcome was the change on the Hamilton Anxiety Scale from baseline to week 8. Patients in both active treatment groups experienced similar improvements on the Hamilton Anxiety Scale (vortioxetine 10mg: -11.66; duloxetine 60mg: -13.87). Response rates on the Hamilton Anxiety Scale were numerically lower for patients on vortioxetine 10mg than on duloxetine. The difference, however, did not reach statistical significance (44.8% vs. 51%; RR 0.88, 95% CI 0.69 to 1.12 [self-calculated]). Likewise, remission rates were lower in the vortioxetine 10mg group than the duloxetine group (20.1% vs. 28.2%; RR 0.71, 95% CI 0.48 to 1.07 [self-calculated]).²⁶ The study did not report any information on time to onset of efficacy, functional capacity, prevention of relapse, or hospitalization rates.

Key Question 2. For outpatients with major depressive disorder or generalized anxiety disorder: do levomilnacipran, vilazodone, or vortioxetine differ in harms compared with other second-generation antidepressants?

Detailed Assessment

In this section we provide a detailed assessment of the comparative risks of harms. Four eligible trials, 3 comparing vortioxetine with duloxetine^{20,21,25} and 1 comparing vortioxetine with

venlafaxine XR¹⁹ reported data on harms (characteristics of included studies are presented in Key Question 1). Three studies included patients with MDD¹⁹⁻²¹; one study, patients with GAD²⁵. Because we presumed similar risks of most adverse events for patients with MDD or GAD, we combined studies of these 2 disorders for the assessment of harms. As for KQ1 on efficacy and effectiveness, we do not report on treatment arms that were outside the FDA-approved dosing ranges.

We did not find any eligible studies comparing levomilnacipran with other second-generation antidepressants.

As described in the methods section, except for serious adverse events, we focused on specific adverse events that occurred with an incidence of at least 5% and were at least twice as frequent as in patients treated with placebo (based on the FDA prescribing information).

Levomilnacipran compared with other second-generation antidepressants

We did not find any eligible studies that directly compared levomilnacipran with other second-generation antidepressants.

Vilazodone compared with other second-generation antidepressants

We present characteristics of the only included RCT comparing vilazodone with citalopram²² in more detail in KQ1 (see Table 3). Just as in KQ1, we do not report results of the treatment arm using vilazodone 20mg because such a dose is outside the approved dosing range.

Overall risk of adverse events

During 10 weeks of treatment, the study found similar overall risks of adverse events for patients treated with vilazodone in comparison to patients treated with citalopram (77.4% vs. 77.0%).²²

Overall discontinuation

Overall discontinuation of treatment during 10 weeks of follow-up was similar between patients treated with vilazodone or citalopram (34.1% vs. 29.1%).²²

Discontinuation because of adverse events

Discontinuation rates because of adverse events were also similar between patients treated with vilazodone and citalopram (8.7% vs. 6.4%).²² The data is insufficient to conclude about differences in discontinuations because of adverse events.

Serious adverse events

Only 10 patients in the entire study experienced serious adverse events: 4 patients in the vilazodone group and 6 patients in the citalopram group (1.4% vs. 2.1%).²² The data is insufficient to conclude about the comparative risks of serious adverse events

Suicidal ideation and behavior

The risk for suicidal ideation as assessed on the Columbia-Suicide Severity Rating Scale was similar between patients on vilazodone and citalopram (18.1% vs. 16.3%).²² One patient attempted suicide in the vilazodone group.

Specific adverse events

Risks for most specific adverse events were similar between the vilazodone and citalopram treatment groups.²² Significantly more patients treated with vilazodone experienced diarrhea (26.5% vs. 10.6%; RR 2.49, 95% CI 1.69 to 3.67 [self-calculated]) and vomiting (6.6% vs. 1.8%; RR 3.73, 95% CI 1.43 to 9.86 [self-calculated]) than patients treated with citalopram.²²

Vortioxetine compared with duloxetine

Overall risk of adverse events

Three fair-quality trials reported overall risks of adverse events.^{20,21,25} A random-effects meta-analysis based on data from 1,164 patients yielded similar overall risks of adverse events for patients treated with vortioxetine and duloxetine (72.4% vs. 71.8%; RR 0.97, 95% CI 0.91 to 1.04; see Figure 6).

Overall risk of discontinuation

Based on a random-effects meta-analysis of 3 eligible multicenter randomized trials^{20,21,25} on a total of 1,173 patients, the overall risk of discontinuation of treatment was similar for patients on vortioxetine compared with those on duloxetine (22.9% vs. 23.3%; RR 0.95, 95% CI 0.77 to 1.18; see Figure 6).

Discontinuation because of adverse events

A random-effects meta-analysis of 3 RCTs^{20,21,25} yielded similar risks of discontinuation because of adverse events for patients treated with vortioxetine or duloxetine (7.0% vs. 9.0%; RR 0.73, 95% CI 0.37 to 1.46; see Figure 6).

Serious adverse events

Three eligible studies provided data on serious adverse events.^{20,21,25} In general, serious adverse events were rare in both treatment groups. A random-effects meta-analysis of the 3 trials yielded indeterminate results regarding differences in risks of serious adverse events in patients treated with vortioxetine or duloxetine (0.6% vs. 0.8%; RR 0.77, 95% CI 0.17 to 3.51; see Figure 6).

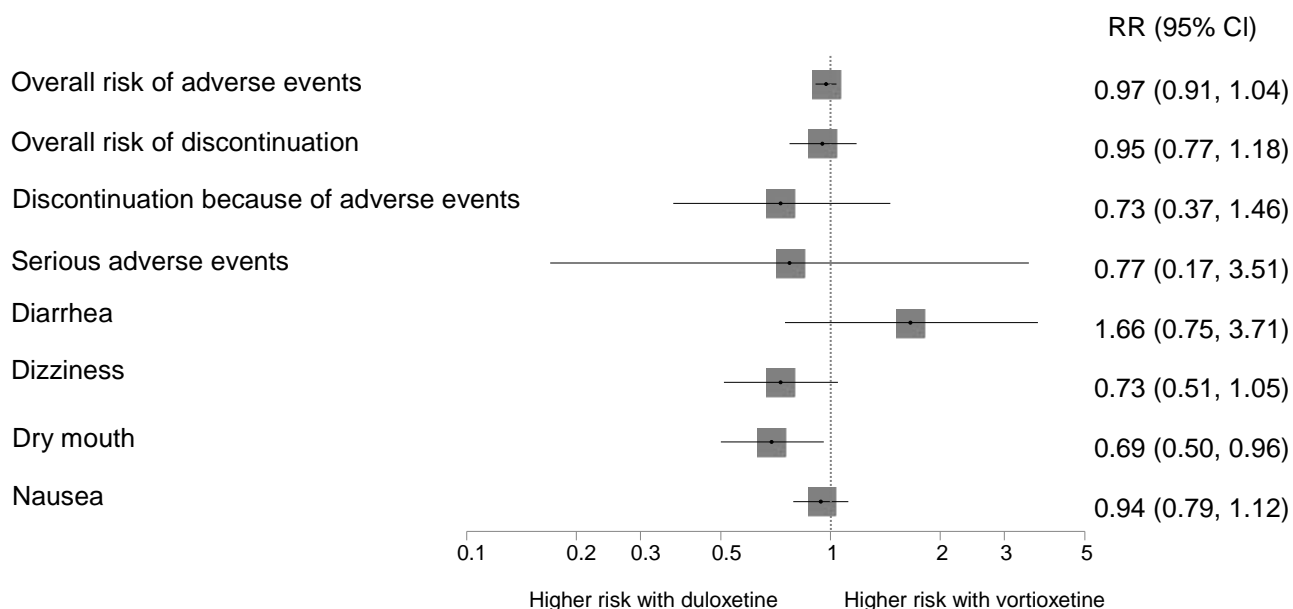
A detailed description of the kinds of serious adverse events was not always available in publications. In 1 study, a patient on vortioxetine experienced suicidal ideation²⁰; in another, a patient on vortioxetine attempted suicide²¹. In patients treated with duloxetine, reported serious adverse events were angina pectoris and somnolence²⁵. No deaths occurred in any of these studies.^{20,21,25} In general, results on differences of specific serious adverse events such as suicidal ideas or behavior are inconclusive.

Specific adverse events

Random-effects meta-analyses of the 3 included RCTs^{20,21,25} rendered similar risks of nausea (30.0% vs. 30.3%; RR 0.94, 95% CI 0.79 to 1.12; see Figure 6 for patients on vortioxetine or duloxetine. Patients treated with vortioxetine experienced lower risks for dizziness (8.4% vs. 10.2%; RR 0.73, 95% CI 0.51 to 1.05; see Figure 6) and dry mouth (9.6% vs. 13.1%; RR 0.69, 95% CI 0.50 to 0.96; see Figure 6) than patients randomized to duloxetine. Results of the meta-analysis on the risk of diarrhea rendered indeterminate findings (see Figure 6). For several other relevant adverse events, data was insufficient to conduct meta-analyses. Studies reported similar

risks for constipation and vomiting. Patients on vortioxetine experienced lower risks of decreased appetite, fatigue, sexual dysfunction, and somnolence. Table 5 depicts risks of these specific adverse events as they were reported in individual trials.

Figure 6: Results of random-effects meta-analyses for harms comparing vortioxetine with duloxetine



Abbreviations: CI, confidence interval; RR, relative risk

Table 6: Relative risks of selected specific adverse events in vortioxetine versus duloxetine trials

Outcome	Study	Study population	RR (95% CI)	Events, vortioxetine	Events, duloxetine
Vomiting	Mahableshwarkar 2014	GAD	0.89 (0.37, 2.13)	9/156	10/154
	Mahableshwarkar 2015 (2)	MDD	0.83 (0.42, 1.65)	20/301	12/150
Constipation	Mahableshwarkar 2014	GAD	1.48 (0.62, 3.52)	12/156	8/154
	Mahableshwarkar 2015 (2)	MDD	0.61 (0.34, 1.10)	22/301	18/150
Decreased appetite	Mahableshwarkar 2014	GAD	0.45 (0.16, 1.26)	5/156	11/154
	Mahableshwarkar 2015 (1)	MDD	0.26 (0.08, 0.92)	3/196	12/207
Sexual dysfunction	Mahableshwarkar 2014	GAD	0.54 (0.34, 0.85)	19/77	34/74
	Mahableshwarkar 2015 (2)	MDD	0.67 (0.45, 0.98)	32/90	25/47
Fatigue	Mahableshwarkar 2014	GAD	0.59 (0.27, 1.31)	9/156	15/154
	Mahableshwarkar 2015 (2)	MDD	0.44 (0.23, 0.86)	15/301	17/150
Somnolence	Mahableshwarkar 2014	GAD	0.42 (0.19, 0.92)	8/156	19/154

Abbreviations: CI, Confidence interval; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; RR, Risk ratio
 (1) Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RS. A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. *Neuropsychopharmacology*. 2015;40:2025-37.

(2) Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology*. 2015;232:2061-70.

Vortioxetine compared with venlafaxine XR

We present characteristics of the only included RCT comparing vortioxetine with venlafaxine XR¹⁹ in more detail in KQ1 (see Table 3). Just as in KQ1, we do not report results of the treatment arm using vortioxetine 5mg because such a dose is outside the approved dosing range.

Overall risk of adverse events

During 6 weeks of treatment, the study found similar overall risks of adverse events for patients treated with vortioxetine in comparison to patients treated with venlafaxine XR (74.0% vs. 75.0%; RR 0.98; 95% CI 0.84 to 1.15 [self-calculated]).¹⁹

Overall discontinuation

Overall discontinuation of treatment during 6 weeks of follow-up was similar between patients treated with vortioxetine or venlafaxine XR (18.8% vs. 18.4%; RR 1.02; 95% CI 0.58 to 1.79 [self-calculated]).¹⁹

Discontinuation because of adverse events

Discontinuation rates because of adverse events were numerically lower for patients treated with vortioxetine than venlafaxine XR. The difference, however, did not reach statistical significance (7.0% vs. 14.2%; RR 0.49; 95% CI 0.21 to 1.15 [self-calculated]).¹⁹

Serious adverse events

Only 3 patients in the entire study experienced serious adverse events: 2 patients in the vortioxetine group (worsening of MDD and varicella zoster infection) and 1 patient in the venlafaxine group (brain tumor).¹⁹ The data is insufficient to conclude about the comparative risks of serious adverse events (2.0% vs. 0.9%; RR 2.26, 95% CI 0.21 to 24.53 [self-calculated]).

Specific adverse events

Risks for specific adverse events were not statistically significantly different between the vortioxetine and venlafaxine XR treatment groups¹⁹. Numerically more patients treated with vortioxetine experienced nausea (38.0% vs. 33.6%; RR 1.13, 95% CI 0.79 to 1.62 [self-calculated]) and vomiting (9.0% vs. 3.5%; RR 2.54, 95% CI 0.81 to 8.00 [self-calculated]) than patients treated with venlafaxine XR. Conversely, numerically fewer patients on vortioxetine reported constipation (3.0% vs 9.7%; RR 0.31, 95% CI 0.09 to 1.07 [self-calculated]) and excessive sweating (10.0% vs. 15.0%; RR 0.66, 95% CI 0.32 to 1.38 [self-calculated]) than patients on venlafaxine XR. Because of the wide confidence intervals, these results have to be interpreted cautiously.

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, socio-demographic factors, and sex), other medications, or comorbidities for which 1 drug (levomilnacipran, vilazodone, or vortioxetine) is more effective or associated with fewer adverse events than another?

Detailed Assessment

Major Depressive Disorder

None of the eligible RCTs¹⁷⁻²¹ that we included for KQ1 and KQ2 assessed differences in subgroups among the active treatment arms.

Generalized Anxiety Disorder

The only eligible RCT for GAD did not assess differences in subgroups between vortioxetine and duloxetine treatment groups.²⁵

LIMITATIONS OF THIS REPORT

As with other types of research, the limitations of this systematic review are important to recognize. Methodological limitations of the review within the defined scope include the exclusion of studies published in languages other than English. While the search of the FDA documents and requests for information from the manufacturers of the drugs is an important step in searching for unpublished studies and supplemental data, another possible limitation is the lack of a specific search for grey literature.

Because of a lack of head-to-head trials, we often had to rely on network meta-analyses to estimate the comparative effectiveness of interventions of interest for the treatment of MDD. Network meta-analyses are an important analytic tool in the absence of direct head-to-head evidence, but they also have limitations. These limitations are reflected in the strength of evidence ratings. For GAD, we were not able to conduct network meta-analyses because of a lack of data.

Finally, publication bias and selective outcome reporting are always potential limitations. Although we searched for unpublished literature, the extent and impact of publication and reporting bias in this body of evidence is impossible to determine.

APPLICABILITY

The scope of this review was limited to trials that enrolled adult patients with MDD or GAD. We did not attempt to review literature on interventions for children with MDD or for patients with subthreshold depression, dysthymia, psychotic depression, or perinatal depression.

The included trials covered populations with mild, moderate, and severe MDD or GAD. Most trial populations, however, excluded patients with medical comorbidities or suicidal ideas and behaviors; few trials included elderly patients. For network meta-analyses, we also limited to patients younger than 65 years of age. Furthermore, all trials were conducted in clinical settings. Results from samples of patients attending a clinic might not apply to members of the general community who suffer from MDD or GAD of the same type. Similarly, we did not find evidence to confirm or refute whether treatments are more or less efficacious for various subgroups: patients characterized by sex, race, or ethnicity, or individuals with coexisting psychiatric conditions.

The samples in many trials had some subjects with the aforementioned subgroup characteristics, even if the main focus was on a different population. For instance, the trials may have included individuals with a history of psychiatric comorbidities but did not report whether interventions were similarly efficacious (or not) for such individuals.

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