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Vortioxetine for depression in adults (Review)

Koesters M, Ostuzzi G, Guaiana G, Breilmann J, Barbui C

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[Intervention Review]

Vortioxetine for depression in adults

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ABSTRACT

Background

Major depressive disorder is a common mental disorder affecting a person's mind, behaviour and body. It is expressed as a variety of symptoms and is associated with substantial impairment. Despite a range of pharmacological and non-pharmacological treatment options, there is still room for improvement of the pharmacological treatment of depression in terms of efficacy and tolerability. The latest available antidepressant is vortioxetine. It is assumed that vortioxetine's antidepressant action is related to a direct modulation of serotonergic receptor activity and inhibition of the serotonin transporter. The mechanism of action is not fully understood, but it is claimed to be novel. Vortioxetine was placed in the category of "Other" antidepressants and may therefore provide an alternative to existing antidepressant drugs.

Objectives

To assess the efficacy and acceptability of vortioxetine compared with placebo and other antidepressant drugs in the treatment of acute depression in adults.

Search methods

We searched Cochrane's Depression, Anxiety and Neurosis Review Group's Specialised Register to May 2016 without applying any restrictions to date, language or publication status. We checked reference lists of relevant studies and reviews, regulatory agency reports and trial databases.

Selection criteria

We included randomised controlled trials comparing the efficacy, tolerability, or both of vortioxetine versus placebo or any other antidepressant agent in the treatment of acute depression in adults.

Data collection and analysis

Two review authors independently selected the studies and extracted data. We extracted data on study characteristics, participant characteristics, intervention details and outcome measures in terms of efficacy, acceptability and tolerability. We analysed intention-to-treat (ITT) data only and used risk ratios (RR) as effect sizes for dichotomous data and mean differences (MD) for continuous data with 95% confidence intervals (CI). Meta-analyses used random-effects models.

Main results

We included 15 studies (7746 participants) in this review. Seven studies were placebo controlled; eight studies compared vortioxetine to serotonin-norepinephrine reuptake inhibitors (SNRIs). We were unable to identify any study that compared vortioxetine to antidepressant drugs from other classes, such as selective serotonin reuptake inhibitors (SSRIs).

Vortioxetine may be more effective than placebo across the three efficacy outcomes: response (Mantel-Haenszel RR 1.35, 95% CI 1.22 to 1.49; 14 studies, 6220 participants), remission (RR 1.32, 95% CI 1.15 to 1.53; 14 studies, 6220 participants) and depressive symptoms measured using the Montgomery-Åsberg Depression Scale (MADRS) (score range: 0 to 34; higher score means worse outcome: MD -2.94, 95% CI -4.07 to -1.80; 14 studies, 5566 participants). The quality of the evidence was low for response and remission and very low for depressive symptoms. We found no evidence of a difference in total dropout rates (RR 1.05, 95% CI 0.93 to 1.19; 14 studies, 6220 participants). More participants discontinued vortioxetine than placebo because of adverse effects (RR 1.41, 95% CI 1.09 to 1.81; 14 studies, 6220 participants) but fewer discontinued due to inefficacy (RR 0.56, 95% CI 0.34 to 0.90, P = 0.02; 14 studies, 6220 participants). The quality of the evidence for dropouts was moderate.The subgroup and sensitivity analyses did not reveal factors that significantly influenced the results.

In comparison with other antidepressants, very low-quality evidence from eight studies showed no clinically significant difference between vortioxetine and SNRIs as a class for response (RR 0.91, 95% CI 0.82 to 1.00; 3159 participants) or remission (RR 0.89, 95% CI 0.77 to 1.03; 3155 participants). There was a small difference favouring SNRIs for depressive symptom scores on the MADRS (MD 1.52, 95% CI 0.50 to 2.53; 8 studies, 2807 participants). Very low quality evidence from eight studies (3159 participants) showed no significant differences between vortioxetine and the SNRIs as a class for total dropout rates (RR 0.89, 95% CI 0.73 to 1.08), dropouts due to adverse events (RR 0.74, 95% CI 0.51 to 1.08) and dropouts due to inefficacy (RR 1.52, 95% CI 0.70 to 3.30).

Against individual antidepressants, analyses suggested that vortioxetine may be less effective than duloxetine in terms of response rates (RR 0.86, 95% CI 0.79 to 0.94; 6 studies, 2392 participants) and depressive symptoms scores on the MADRS scale (MD 1.99, 95% CI 1.15 to 2.83; 6 studies; 2106 participants). Against venlafaxine, meta-analysis of two studies found no statistically significant differences (response: RR 1.03, 95% CI 0.85 to 1.25; 767 participants; depressive symptom scores: MD 0.02, 95% CI -2.49 to 2.54; 701 participants). In terms of number of participants reporting at least one adverse effect (tolerability), vortioxetine was better than the SNRIs as a class (RR 0.90, 95% CI 0.86 to 0.94; 8 studies, 3134 participants) and duloxetine (RR 0.89, 95% CI 0.84 to 0.95; 6 studies; 2376 participants). However, the sensitivity analysis casts some doubts on this result, as only two studies used comparable dosing.

We judged none of the studies to have a high risk of bias for any domain, but we rated all studies to have an unclear risk of bias of selective reporting and other biases.

Authors' conclusions

The place of vortioxetine in the treatment of acute depression is unclear. Our analyses showed vortioxetine may be more effective than placebo in terms of response, remission and depressive symptoms, but the clinical relevance of these effects is uncertain. Furthermore, the quality of evidence to support these findings was generally low. In comparison to SNRIs, we found no advantage for vortioxetine. Vortioxetine was less effective than duloxetine, but fewer people reported adverse effects when treated with vortioxetine compared to duloxetine. However, these findings are uncertain and not well supported by evidence. A major limitation of the current evidence is the lack of comparisons with the SSRIs, which are usually recommended as first-line treatments for acute depression. Studies with direct comparisons to SSRIs are needed to address this gap and may be supplemented by network meta-analyses to define the role of vortioxetine in the treatment of depression.

PLAIN LANGUAGE SUMMARY

Vortioxetine for the treatment of depression in adults

Why is this review important?

Many people suffer from major depression. Major depression is a serious illness that can cause significant distress both to patients and their families. Major depression affects people's work and relationships, but can also affect people physically, for example by changing concentration or appetite. Available antidepressant medicines are not always effective in treating major depression and may also have unpleasant side effects. This review compares a new antidepressant, vortioxetine, to placebo (a pretend treatment, e.g. sugar tablet) and other antidepressants. It is assumed that vortioxetine works differently from other available antidepressants and it is important to know if it is an effective treatment and a possible alternative for already available treatments.

Who will be interested in this review?

People affected by major depression and their families, general practitioners (GPs), psychiatrists, and pharmacists and other professionals working in adult mental health services.

What questions does this review aim to answer?

Is vortioxetine more effective than placebo in treating individual with an episode of major depression?
Is vortioxetine more or less effective than other available antidepressant treatments?
Do more or fewer people stay in treatment when treated with vortioxetine compared to placebo or other antidepressants?
Do more or fewer people have side effects when treated with vortioxetine compared to other antidepressants?

Which studies were included in the review?

In May 2016, we searched electronic medical databases to find trials that compared vortioxetine to placebo or other antidepressants. We included only studies that used a randomised controlled design (where people were randomly put into one of two or more treatment groups) and had adults (aged over 18 years) with a diagnosis of major depression. We included 15 trials, involving 7746 participants in the review.

What does the evidence from the review tell us?

The quality of the evidence ranged from very low to moderate, depending on the outcome (what symptom or effect was measured) and the comparison. Vortioxetine was more effective than placebo, but it was not more effective than other commonly used antidepressants. The studies found no difference in people stopping their treatment compared to placebo or other antidepressants. Vortioxetine was only compared to one type of medicine (called SNRIs) and not compared to the most frequently prescribed antidepressants. The outcomes varied markedly across studies.

What should happen next?

No firm conclusion on vortioxetine can be made. Vortioxetine was effective in treating acute major depression, but did not show a clear advantage in comparison with some treatments which are already available. Conclusions are also made difficult because comparisons to the most frequently prescribed antidepressants (called SSRIs) are lacking. Furthermore, it is unclear if vortioxetine has an advantage in specific side effects associated with commonly prescribed antidepressants, for example sexual problems. These questions should be addressed in future studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Vortioxetine compared to Placebo for adults with Major Depressive Disorder

Vortioxetine compared to Placebo for adults with Major Depressive Disorder

Patient or population: adults with Major Depressive Disorder
Setting: Inpatients and outpatients
Intervention: Vortioxetine
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Vortioxetine				
Response assessed with: reduction of at least 50% on the HAMD scale or MADRS scale, or any other score 1 or 2 on CGI-I follow up: range 6 weeks to 8 weeks	Study population 356 per 1,000	480 per 1,000 (434 to 530)	RR 1.35 (1.22 to 1.49)	6220 (14 RCTs)	⊕⊕⊖⊖ LOW [1,2]	All studies were sponsored by the pharmaceutical companies that manufacture vortioxetine. Small difference favouring vortioxetine.
Total number of drop-outs follow up: range 6 weeks to 8 weeks	Study population 160 per 1,000	168 per 1,000 (149 to 190)	RR 1.05 (0.93 to 1.19)	6220 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	No difference between vortioxetine and placebo.
Remission assessed with: 7 points or less on the 17-item HAM-D and 8 points or less for longer HAM-D versions; 10 or less points on the MADRS; score 1 or 2 on CGI-S follow up: range 6 weeks to 8 weeks	Study population 224 per 1,000	299 per 1,000 (258 to 343)	RR 1.33 (1.15 to 1.53)	6217 (14 RCTs)	⊕⊕⊖⊖ LOW [1,2]	Small difference favouring vortioxetine.
Depressive Symptoms assessed with: MADRS score (score range: 0-34; higher score means worse outcome) follow up: range 6 weeks to 8 weeks	The change in depressive symptoms score ranged from 10.8 to 15.9 points	The change was 2.94 points higher (1.8 higher to 4.07 higher)	-	5566 (14 RCTs)	⊕⊖⊖⊖ VERY LOW [1,3]	Small difference favouring vortioxetine.

Drop-out due to adverse events follow up: range 6 weeks to 8 weeks	Study population		RR 1.41 (1.09 to 1.81)	6220 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Small difference favouring placebo.
	38 per 1,000	53 per 1,000 (41 to 68)				
Drop-out due to inefficacy follow up: range 6 weeks to 8 weeks	Study population		RR 0.56 (0.34 to 0.90)	6220 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Small difference favouring vortioxetine.
	31 per 1,000	18 per 1,000 (11 to 28)				
Tolerability	Study population		RR 1.12 (1.07 to 1.16)	6182 (14 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Small difference favouring placebo
	564 per 1,000	632 per 1,000 (603 to 654)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] A serious risk of bias is present, as about 30% of the studies showed an overall dropout rate above 20%, evidence was downgraded by one level
[2] A moderate degree of heterogeneity (I-squared 30-60%) is present, evidence was downgraded by one level
[3] A substantial degree of heterogeneity (I-squared 60-90%) is present, evidence was downgraded by two levels

Summary of findings 2. Vortioxetine compared to SNRIs for adults with Major Depressive Disorder

Vortioxetine compared to SNRIs for adults with Major Depressive Disorder

Patient or population: adults with Major Depressive Disorder
Setting: Inpatients and outpatients
Intervention: Vortioxetine
Comparison: SNRIs

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments

	Risk with SNRIs	Risk with Vortioxetine				
Response assessed with: assessed with: reduction of at least 50% on the HAMD scale or MADRS scale, or any other score 1 or 2 on CGI-I follow up: range 6 weeks to 8 weeks	Study population 577 per 1,000	 525 per 1,000 (473 to 577)	RR 0.91 (0.82 to 1.00)	3159 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,2]	All studies were sponsored by the pharmaceutical companies that manufacture vortioxetine. No difference between vortioxetine and SNRIs.
Total number of drop-outs follow up: range 6 weeks to 8 weeks	Study population 212 per 1,000	 189 per 1,000 (155 to 229)	RR 0.89 (0.73 to 1.08)	3159 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,3]	No difference between vortioxetine and SNRIs.
Remission assessed with: 7 points or less on the 17-item HAM-D and 8 points or less for longer HAM-D versions; 10 or less points on the MADRS; score 1 or 2 on CGI-S follow up: range 6 weeks to 8 weeks	Study population 370 per 1,000	 329 per 1,000 (285 to 381)	RR 0.89 (0.77 to 1.03)	3155 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,2]	No difference between vortioxetine and SNRIs.
Depressive Symptoms assessed with: MADRS score (score range: 0-34; higher score means worse outcome) follow up: range 6 weeks to 8 weeks	The change in depressive symptoms score ranged from 14.1 to 23.4 points	The change was 1.52 points lower (0.5 lower to 2.53 lower)	-	2807 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,2]	Small difference favouring SNRIs.
Drop-out due to adverse events follow up: range 6 weeks to 8 weeks	Study population 97 per 1,000	 72 per 1,000 (50 to 105)	RR 0.74 (0.51 to 1.08)	3159 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,2,3]	No difference between vortioxetine and SNRIs.
Drop-out due to inefficacy follow up: range 6 weeks to 8 weeks	Study population 14 per 1,000	 21 per 1,000 (10 to 45)	RR 1.52 (0.70 to 3.30)	3159 (8 RCTs)	⊕⊝⊝⊝ VERY LOW [1,4]	No difference between vortioxetine and SNRIs.
Tolerability	Study population 690 per 1,000	 621 per 1,000 (593 to 648)	RR 0.90 (0.86 to 0.94)	3134 (8 RCTs)	⊕⊕⊝⊝ LOW [1]	Small difference favouring vortioxetine

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] A very serious risk of bias is present as 60% of the studies had more than 20% dropouts overall, evidence was downgraded by two levels
[2] A moderate degree of heterogeneity (I-squared 30-60%) is present, evidence was downgraded by one level
[3] The 95% CI crossed both 1 (no differences) and 0.75 (appreciable benefit for vortioxetine), evidence was downgraded by one level
[4] The 95% CI crossed 1 (no differences), 0.75 (appreciable benefit for vortioxetine) and 1.25 (appreciable benefit for SNRIs). Outcome is very imprecise: evidence was downgraded by two levels

BACKGROUND

Description of the condition

Major depressive disorder (MDD) affects a person's mind, behaviour and body and is expressed in a variety of symptoms. The core features are depressed mood and loss of interest or pleasure. Other diagnostic criteria include significant changes in bodyweight, decreased or increased appetite, sleep disturbances, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, reduced concentration and suicidal ideation (APA 2013). According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a person must have symptoms for at least two weeks (APA 2013). The core features of major depression have not been changed from DSM-IV to DSM-5. Although there are some differences in the diagnosis of depression between DSM and International Classification of Diseases (ICD), diagnoses of major depression according to DSM-IV seems to be congruent with severe or moderate depressive episodes according to ICD-10 (Saito 2010).

MDD is a common mental disorder, but prevalence rates vary markedly across countries. Lifetime prevalence was estimated at 14.6% on average in high-income countries and 11.1% in low-income countries, with a female:male ratio of about 2:1 (Bromet 2011). MDD is associated with substantial impairment. According to the Global Burden of Disease study, MDD is the second leading cause of disability worldwide (Vos 2012).

Description of the intervention

A variety of pharmacological and non-pharmacological treatment options is available for the treatment of MDD. Pharmacological treatment options comprise monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) or heterocyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine (-noradrenaline) reuptake inhibitors (SNRIs), and other antidepressant agents (e.g. mirtazapine, bupropion, reboxetine, agomelatine), as well herbal products (e.g. hypericum). Current guidelines for depression recommend the use of an antidepressant or psychological treatment for people with moderate depression (APA 2010; NICE 2009) as first-line treatment. According to these guidelines, the effectiveness between classes of antidepressants is similar. However, SSRIs are recommended over TCAs and MAOIs due to their favourable adverse effect profile (APA 2010; NICE 2009). SSRIs have now become the most prescribed antidepressant class in most parts of the world (Bauer 2008; Grover 2013; Zhang 2013).

Vortioxetine was licensed for the treatment of depression by the Food and Drugs Administration (FDA) in September 2013 in the USA (FDA 2014) and by the European Medicines Agency (EMA) in December 2013 for the EU (EMA 2014). Despite the similarities to SSRIs, the mechanism of action of vortioxetine is claimed to be novel (see How the intervention might work). According to the ATC classification of the World Health Organization (WHO), vortioxetine is placed in the category of "Other" antidepressants (WHO 2016). Due to the recent marketing authorisation, clinical experience and data on clinical use of vortioxetine is very limited at this time.

How the intervention might work

The mechanism of action of vortioxetine is not fully understood, but it is assumed to be related to a direct modulation of serotonergic receptor activity and inhibition of the serotonin transporter. Vortioxetine is an antagonist to 5-HT_3, 5-HT_{1D} and 5-HT_7 receptors, a partial agonist to the 5-HT_{1B} receptor and a 5-HT_{1A} receptor agonist (EMA 2014a). However, it is unclear if and how these mechanism contribute to an antidepressant effect. It is hypothesised that serotonin transporter inhibition, combined with the several other actions of vortioxetine at 5-HT receptors, mainly at 5-HT_3 receptors, enhances the release of serotonin and modulates the release of other neurotransmitters within various brain circuits (enhanced release of norepinephrine, dopamine, histamine, acetylcholine and glutamate; reduced gamma-aminobutyric acid (GABA) signalling). These actions could improve the efficiency of information processing in malfunctioning brain circuits by facilitating long-term potentiation, neuroplasticity and increased firing of pyramidal neurons (Du Jardin 2016; Pehrson 2016; Stahl 2015).

Why it is important to do this review

Despite the common use of antidepressants and the variety of available treatment options, there is still an ongoing debate about the use of antidepressants in general as some studies show modest effects compared to placebo (Kirsch 2008). A significant proportion of people do not achieve remission with current treatments (Pigott 2011). Furthermore, although the adverse effect profile of SSRIs is in general judged favourable over TCAs or MAOIs, many people are dropping out of antidepressant treatment (Pigott 2011), mainly due to adverse effects (Bull 2002). Thus, there is still room for improvement of the pharmacological treatment of depression.

Another subject of debate is the comparative effects of modern antidepressants. One multiple-treatment meta-analysis of 12 new-generation antidepressant drugs concluded that sertraline and escitalopram may be more favourable in terms of efficacy and acceptability compared to the other included antidepressants (Cipriani 2009). Notably, this finding could not be replicated in another comprehensive review (Gartlehner 2011). The latter review concluded that there are no substantial differences in efficacy between the antidepressants, but that antidepressants differ in onset of action and adverse events (Gartlehner 2011).

Vortioxetine was approved in late 2013 for the USA and EU and is currently the latest available antidepressant. Randomised controlled trials (RCTs) comparing vortioxetine to placebo or other antidepressants have been published. Several systematic reviews and meta-analyses have been published on the efficacy and tolerability on vortioxetine. The first meta-analysis included seven studies comparing vortioxetine to placebo (Berhan 2014). One systematic narrative review gave an overview of the vortioxetine studies and reported results of 10 RCTs in adults with major depression without pooling the results (Citrome 2014). Two meta-analyses did not conduct a systematic review of the data. The first pooled analysis selected 11 short-term placebo-controlled trials and five long-term open-label studies to evaluate the safety and tolerability of vortioxetine (Baldwin 2016). The second pooled analysis analysed a selected subset of five studies to examine the effect of vortioxetine on quality of life (Florea 2015). Furthermore, 11 studies were included in an indirect comparison of vortioxetine, duloxetine, sertraline, vilazodone, levomilnacipram and escitalopram (Citrome 2016). Two other meta-analyses focused on a subset of a specific dose of vortioxetine 5 mg (Fu 2015) or 10 mg (Li 2016) compared to placebo. However, another meta-analysis, based on an analysis of 11 studies, found no effect differences

related to dosing (Meeker 2015). This meta-analysis included comparisons of vortioxetine and placebo as well as vortioxetine and active comparators, but it included subtherapeutic doses below 5 mg. In sum, these reviews agree that vortioxetine has a significant advantage compared to placebo in terms of efficacy, but found no advantage compared to other available antidepressants.

A summary of the FDA review of vortioxetine is also available (Zhang 2015). The FDA review included 10 short-term placebo-controlled trials and concluded that vortioxetine demonstrated efficacy in six of the included trials, but reported that only vortioxetine 20 mg/day showed superiority over placebo in US trials and showed smaller effects in general in US populations. The most recent meta-analysis, which was co-authored by employees of the manufacturers of vortioxetine, analysed an almost identical dataset and included data from treatment arms in the approved dose range of 11 short-term studies which had results published on ClinicalTrials.gov (Thase 2016). Most analyses were conducted with aggregated data, but additional individual participant data were used. Apparently, the analyses did not follow an a priori defined protocol. However, the analyses are in line with the findings from previous reviews, showing a statistically significant advantage of vortioxetine compared to placebo, but a clear dose-response relationship could not be established. It also confirms the findings of smaller effects in US studies. Thus, despite several attempts to synthesise available literature on vortioxetine, a practical interpretation of data from current systematic reviews may be limited by comprehensiveness issues (lack of thorough search for unpublished data, selective inclusion of trials in the analyses), and possible conflicts of interest. Our review provides an independent, comprehensive and up-to-date summary of the available evidence of the efficacy and acceptability of vortioxetine compared to placebo and other active pharmacological treatment options.

OBJECTIVES

To assess the efficacy and acceptability of vortioxetine compared with placebo and other antidepressant drugs in the treatment of acute depression in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs but excluded quasi-RCTs. For trials with a cross-over design, we considered only the results from the first randomisation period. We included cluster-RCTs if sufficient information was available to account for the clustering (see Unit of analysis issues).

Types of participants

Characteristics

Participants of both sexes, of any ethnicity, and aged 18 years and older.

Diagnosis

Participants with a primary diagnosis of unipolar major depression according to DSM-III (APA 1980), DSM- III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000), DSM-5 (APA 2013), ICD-10 (WHO 1992), Feighner (Feighner 1972) or Research Diagnostic Criteria (Spitzer 1978), and Chinese Classification of Mental Disorders (CCMD-3, Chinese Society of Psychiatry 2001). We excluded studies of people with treatment-resistant depression, defined as inadequate treatment response to at least four weeks of adequate antidepressant treatment.

Comorbidities

We included studies with people with comorbid psychiatric disorders. We excluded antidepressant trials in people with depression with a serious concomitant physical illness (e.g. myocardial infarction, diabetes, cancer, etc.).

Setting

Any setting.

Subset data

Based on National Institute for Health and Care Excellence (NICE) guidelines for the treatment of depression in adults (NICE 2009), we included studies in which less than 20% of the included participants had bipolar depression.

We included studies with relevant subsets of data (e.g. some participants aged below 18 years) if the data were available for the relevant subset and the randomisation was stratified by the criterion in question. Inclusion of these studies was examined in sensitivity analyses.

Types of interventions

Experimental intervention

- Vortioxetine monotherapy. To increase the clinical applicability of the review, we excluded treatment arms employing dosages below the lowest effective dose of 5 mg/day (EMA 2014b). We included treatment arms with fixed and flexible dosing schemes. Fixed doses are set a priori and are independent from participant criteria, while in flexible dosing schemes the dose is adapted according predefined criteria, for example, insufficient response.

Comparator intervention

- Placebo.
- Another antidepressant as monotherapy, including:
  - conventional TCA or heterocyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, dosulepin/dothiepin, doxepin, imipramine, lofepramine, maprotiline, nortriptyline, protriptyline, trimipramine);
  - SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, escitalopram);
  - SNRIs (venlafaxine, duloxetine, milnacipran);
  - MAOIs (phenelzine, isocarboxazide, tranylcypromine, moclobemide, brofaromine);
  - other antidepressant agents (mirtazapine, bupropion, reboxetine, agomelatine) or non-conventional antidepressive agents (herbal products such as hypericum).

We applied no restrictions on dosage of the comparators, but we conducted sensitivity analyses and excluded studies with unequal dosing.

Types of outcome measures

We included studies that meet the above inclusion criteria regardless of whether they report on the following outcomes.

Primary outcomes

- Response to treatment: the primary efficacy outcome was the number of participants who responded to acute treatment, as defined by a reduction of at least 50% on the Hamilton Depression Rating Scale (HAM-D) scale (Hamilton 1960) or Montgomery-Åsberg Depression Scale (MADRS; Montgomery 1979), or any other depression scale, or "much or very much improved" (score 1 or 2) on Clinical Global Impression - Improvement (CGI-I) (Guy 1970). We did not consider other definitions of response in this Cochrane Review.

Where more than one scale was provided, we gave preference as listed. We used response rate instead of a continuous symptom score for the primary efficacy analysis to make the interpretation of results easier (Guyatt 1998).

- Total number of dropouts: primary outcome measuring acceptability was the total number of participants dropping out during the trial as a proportion of the total number of randomised participants.

Secondary outcomes

- Remission: number of participants who achieved remission. We defined remission a priori as:
  - 7 points or less on the 17-item HAM-D and as 8 points or less for all the other longer versions of HAM-D;
  - 10 or less points on the MADRS;
  - "not ill or borderline mentally ill" (score 1 or 2) on Clinical Global Impression - Severity (CGI-S) (Guy 1970) at endpoint.

We did not consider other definitions of remissions in this Cochrane Review.

- Depressive symptoms: endpoint mean scores, or mean change scores at endpoint on HAM-D, MADRS, or any other depression rating scale score.
- Dropouts due to adverse events: number of participants who dropped out due to adverse events during the trial as a proportion of the total number of randomised participants.
- Dropouts due to inefficacy: number of participants who dropped out due to inefficacy during the trial as a proportion of the total number of randomised participants.
- Tolerability: evaluated using the total number of participants experiencing at least one adverse event.

We collected any data on specific adverse effects and reported these data in tables. However, due to the poor reporting in RCTs (Zorzela 2014), we did not summarise these data in meta-analyses.

Although the effect on cognition is a relevant outcome for people treated with psychopharmacological treatments, we decided to exclude cognition as an outcome. According to the EMA, cognition was not systematically assessed (EMA 2014a). The EMA report on vortioxetine indicated that only three studies reported this outcome and that a meta-analysis by the manufacturer of these studies had outcome reporting bias (EMA 2014a). Furthermore, the EMA report pointed out that it was not possible to distinguish between an effect on cognition and a relief of depressive symptoms, because no active comparator was included.

Timing of outcome assessment

Our primary outcomes were the acute phase treatment response (between four and 12 weeks). When studies reported efficacy data at different time points, we gave preference to the time point closest to eight weeks.

Hierarchy of outcome measures

We included efficacy data measured by HAM-D (Hamilton 1960), MADRS (Montgomery 1979), or any other depression scale. Response or remission rates may also be based on CGI-I scores (Guy 1970) or a combination of these outcomes. Where more than one criterion was provided, we planned to use the data according to the following hierarchy: HAM-D, MADRS, other depression scales and CGI and combination of these in cases of remission and response rates. However, due to the reporting of the MADRS (see Description of studies) we gave preference to MADRS outcomes (see Differences between protocol and review). We did not include CGI scores as a continuous outcome. The HAM-D scale is available in various versions which differ in the number of included items. The versions with 17, 21 or 24 items are the most common and we gave preference to these in this order. Studies may also use different criteria for response or remission. We gave preference according to the list described in the corresponding outcome section (see Primary outcomes; Secondary outcomes).

Search methods for identification of studies

Cochrane Collaboration Depression, Anxiety and Neurosis Review Group's Specialized Register (CCDANCTR)

The Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK: a References Register and a Studies Register. The CCDANCTR-References Register contains over 37,000 reports of RCTs in depression, anxiety and neurosis. Approximately 60% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers using unique Study ID tags. Coding of trials is based on the EU-PSI coding manual, using a controlled vocabulary (see Cochrane Collaboration Depression, Anxiety & Neurosis Group for further details). Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (from 1950), Embase (from 1974) and PsycINFO (from 1967); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials are also sourced from international trials registers via the WHO trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, handsearching of key journals, conference proceedings, and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies (used to identify RCTs) can be found on the Group's website.

Electronic searches

We performed the following electronic searches with no restrictions on date, language or publication status.

- **CCDANCTR-Studies Register** using the following controlled search terms:

Condition = depress*
AND
Intervention = Vortioxetine or "Lu AA21004"

- **CCDANCTR-References Register** using a more sensitive set of free-text terms to identify additional untagged/uncoded reports of RCTs:

Free-text = (depress* or dysthymi* or "mood disorder*" or "affective disorder*" or "affective symptom*") and (Vortioxetine or "Lu AA21004" or LuAA21004 or Brintellix)

- International trial registries via the WHO trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies, together with the trial registries of relevant pharmaceutical companies:
  - Lundbeck Clinical Trials Registry;
  - Takeda Clinical Study Protocols and Results.
- Regulatory databases including those of the FDA in the US (Drugs@FDA) and the EMA (EMA).

Searching other resources

Reference lists

We checked the reference lists of all included studies and relevant systematic reviews to identify additional studies missed from the original electronic searches (e.g. unpublished or in-press citations). Also, we conducted a cited reference search on the Web of Science.

Correspondence

We contacted trialists and subject experts for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors (GO, MK) independently screened titles and abstracts for inclusion of all studies identified by the search and coded them as 'potentially eligible.' We retrieved the full-texts of study reports/publications rated as 'potentially eligible' by one or both review authors. Two review authors (GO, MK) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies (see Characteristics of excluded studies table). We resolved any disagreements through discussion or, if required, by consulting a third review author (CB). We collated multiple reports of the same study and included them a single study.

Data extraction and management

We used a data collection form which had been piloted on at least one study in the review to extract study characteristics and outcome data. Two review authors (CB, MK) independently extracted study characteristics and outcome data from included studies. We extracted the following study characteristics.

- Methods: blinding, total duration of study, details of 'run in' periods, number of study centres and location, study setting, withdrawals and date of study.
- Participants: sample size, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications, excluded medications, dose and dosing scheme (fixed versus flexible).
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial and notable conflicts of interest of trial authors.

We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third review author (CB). One review author (MK) transferred data into Review Manager 5 (RevMan 2014). Two review authors (GO, JB) double checked the data entered for correctness by comparing the data presented in the systematic review with the study reports. A third review author (CB) spot-checked study characteristics for accuracy against the trial report.

Main planned comparisons

We combined the comparators (see Types of interventions) into classes in the meta-analyses. Therefore, the main planned comparisons were:

- vortioxetine versus placebo;
- vortioxetine versus TCAs/heterocyclics;
- vortioxetine versus SSRIs;
- vortioxetine versus SNRIs;
- vortioxetine versus MAOIs;
- vortioxetine versus other antidepressant agents.

Wherever suitable, we presented data with substances as subgroups within each class.

Assessment of risk of bias in included studies

Two review authors (MK, GO) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving a third review author (CB). We assessed the risk of bias in the included studies according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We judged potential sources of bias as 'high,' 'low' or 'unclear' and provided supporting quotation a from the study report together with a justification for our judgement in the 'Risk of bias' table. The risk of bias judgements were summarised across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for treatment discontinuation may be different than for a participant-reported scale). Where information on risk of bias relates to unpublished

data or correspondence with a trial author, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

Dichotomous data

We analysed dichotomous data as risk ratios (RRs), because RRs are more intuitive in their interpretation than odds ratios (Grant 2014), with 95% confidence intervals (CI). Where reported intention-to-treat (ITT) analysis was based on a 'modified' ITT not including all dropouts (e.g. leaving out dropouts without postbaseline assessment), we applied a conservative approach and considered these dropouts as non-responders or non-remitters (i.e. assumed they would have experienced the negative outcome by the end of the trial, e.g. failure to respond to treatment).

Continuous data

We analysed continuous data as mean difference (MD) with 95% CI, if all studies reported the necessary data from HAM-D-scales as an outcome. In cases that data from different scales were combined, we used standardised mean difference (SMD) with 95% CI. We entered and presented data with a consistent direction of effect. Data were analysed as endpoint data. We combined endpoint and change scores only if data were analysed as MD. Analyses were conducted with ITT data as reported (e.g. data from last observation carried forward (LOCF) or mixed model for repeated measurements (MMRM) methods).

We conducted meta-analyses only where this was meaningful (i.e. if the treatments, participants and underlying clinical question were similar enough for pooling to make sense).

Unit of analysis issues

Cluster-randomised controlled trials

Cluster-RCTs were eligible for inclusion if sufficient information was available to account for the clustering (see Differences between protocol and review).

Cross-over trials

For trials with a cross-over design, we considered only the results from a first randomisation period (see Differences between protocol and review).

Studies with multiple treatment groups

If more than one treatment arm was reported in a single trial, we only included the relevant treatment arms. In case of multiple relevant treatment arms (e.g. different dosages), we combined these treatment arms into a single group. For dichotomous outcomes, we summarised data across groups; while for continuous outcomes, we combined means and standard deviations according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 7.7.3.8, Higgins 2011).

In case of relevant treatment arms that could not be combined (e.g. different SSRIs as comparators), we divided the sample size of the shared group so that the two arms were treated as independent comparisons.

Dealing with missing data

We contacted study authors or study sponsors to verify key study characteristics and missing outcome data. Attempts to contact authors and sponsors were documented, as well as additional data we received in these correspondences.

In the absence of supplemental data from the authors, we planned to calculate the SDs of the HAM-D (or any other depression scale) and response/remission rates according to validated imputation methods (Furukawa 2005; Furukawa 2006). We planned to examine the validity of these imputations in sensitivity analyses.

Assessment of heterogeneity

Variations in participants and interventions lead to clinical heterogeneity. We extracted basic study characteristics (see Data collection and analysis) from the studies and described these in the Characteristics of included studies tables. A decision was then made as to whether studies were similar enough to combine in meta-analyses.

We quantified statistical heterogeneity of the studies using the I^2 statistic and Chi^2 test. As the Chi^2 test is known to have low power, we used P = 0.10 as a threshold for statistical significance. Our interpretation of the I^2 statistic followed the recommendation of the *Cochrane Handbook for Systematic Reviews of Interventions* and we considered the I^2 statistic as:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We also assessed heterogeneity by visual inspection of forest plots.

Assessment of reporting biases

Publication bias was scrutinised by visual inspection of funnel plots if we include more than 10 studies in the analysis of the outcome in question.

Data synthesis

We used a random-effects model in our primary analysis. We expected some heterogeneity in the studies included and the random-effects model incorporates the variance between studies in the model. As a result, CIs are wider. The random-effects model has the highest generalisability in an empirical examination of summary effect measures for meta-analyses (Furukawa 2002). We routinely examined the robustness of this summary measure by checking the results under a fixed-effect model. Material differences between the models were reported.

Subgroup analysis and investigation of heterogeneity

We only conducted subgroup and sensitivity analysis for the primary outcomes.

A priori, we planned to perform the following subgroup analyses.

- Vortioxetine dosing: fixed versus flexible dosing schemes.
- Treatment setting: primary care versus inpatient care versus outpatient care.

- Older people (aged more than 65 years): included versus excluded.

Sensitivity analysis

We planned to perform the following sensitivity analyses to examine the robustness of the effect size.

- Exclusion of trials with unequal dosing. We defined comparability of doses by comparing the percentage of the maximum licensed daily dose in both groups (e.g. vortioxetine 10 mg/day (50% of 20 mg/day) equals fluoxetine 40 mg/day (50% of 80 mg/day)).
- Exclusion of studies that did not employ a double-blind approach.
- Exclusion of studies with subsets of people with bipolar disorders.
- Exclusion of trials with dropout rates of more than 20% in one of the treatment arms included.
- Exclusion of studies with imputed data.
- Exclusion of studied sponsored by the manufacturer of vortioxetine.

'Summary of findings' table

We employed the GRADE approach to interpret findings (Langendam 2013) and used GRADEpro to import data from Review Manager 5 (RevMan 2014) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined and the sum of available data on the outcomes.

For each comparison, we reported the primary outcomes (response and total number of dropouts) and secondary outcomes (remission, depressive symptoms, dropouts due to adverse events, dropouts due to inefficacy and participants experience at least one adverse event).

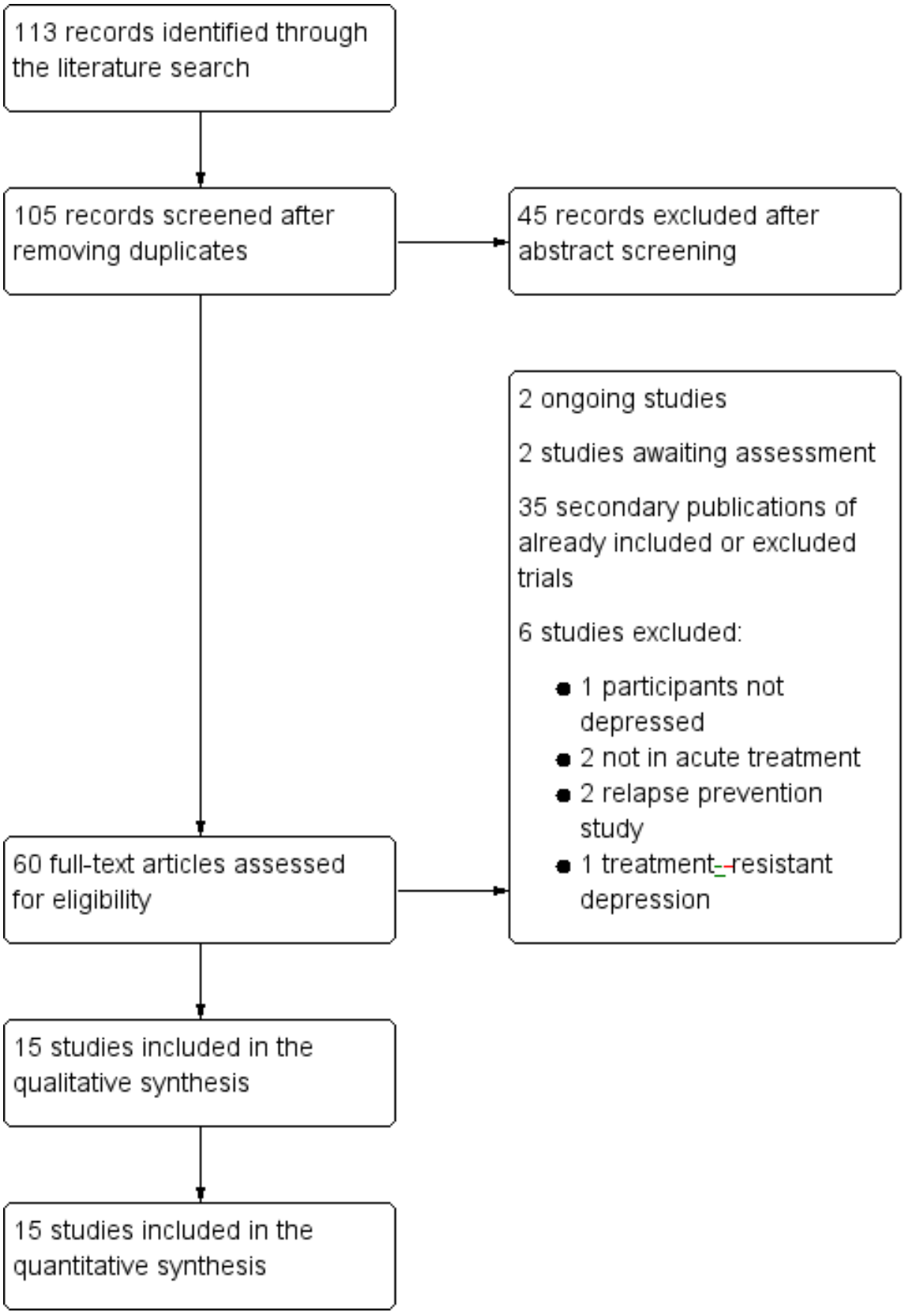
RESULTS

Description of studies

Results of the search

The literature search identified 113 records including eight duplicates. We excluded 45 of the remaining 105 records based on the abstracts. We retrieved 60 full-text articles for detailed examination, which led to the exclusion of 45 records. The majority (35 trials) were secondary publications of already included or excluded trials. Two studies did not meet our inclusion criterion for acute treatment (Jacobsen 2015a; Jacobsen 2015b); two were relapse prevention studies (Boulenger 2012; NCT02371980); one trial did not meet our criterion for depression because it randomised remitted participants and healthy controls only (Browning 2014); and one study randomised participants to vortioxetine or agomelatine after an inadequate response to at least six weeks of SSRI or SNRI treatment (Montgomery 2014). We identified two ongoing studies (NCT02294305; NCT02389816) which may fulfil the inclusion criteria of this review and two studies are awaiting assessment as there are no published results (NCT02272517; NCT02279966). Request of additional information by the manufactures or the authors was not necessary. The literature search was last updated in May 2016 (see Figure 1; Characteristics of excluded studies table).

Figure 1. Study flow diagram.



Included studies

Fifteen studies were included in this systematic review (Alvarez 2012; Baldwin 2012; Boulenger 2014; Henigsberg 2012; Jacobsen 2015; Jain 2013; Katona 2012; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b; Mahableshwarkar 2015c; McIntyre 2014; NCT01255787; Takeda 2011; Wang 2015). Two of these were unpublished trials carried out by a pharmaceutical company (Takeda) (NCT01255787; Takeda 2011). (See Characteristics of included studies table).

Design

All included studies were randomised trials and applied double-blind methodology. Seven studies were three-armed with vortioxetine, an active comparator and placebo (Alvarez 2012; Baldwin 2012; Boulenger 2014; Katona 2012; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b). Eight studies were two-armed, among these seven studies were placebo-controlled (Henigsberg 2012; Jacobsen 2015; Jain 2013; Mahableshwarkar 2015c; McIntyre 2014; NCT01255787; Takeda 2011), and one study was active controlled only (Wang 2015).

Trial duration

Two studies lasted six weeks (Alvarez 2012; Jain 2013), and 13 studies lasted eight weeks (Baldwin 2012; Boulenger 2014; Henigsberg 2012; Jacobsen 2015; Katona 2012; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b; Mahableshwarkar 2015c; McIntyre 2014; NCT01255787; Takeda 2011; Wang 2015).

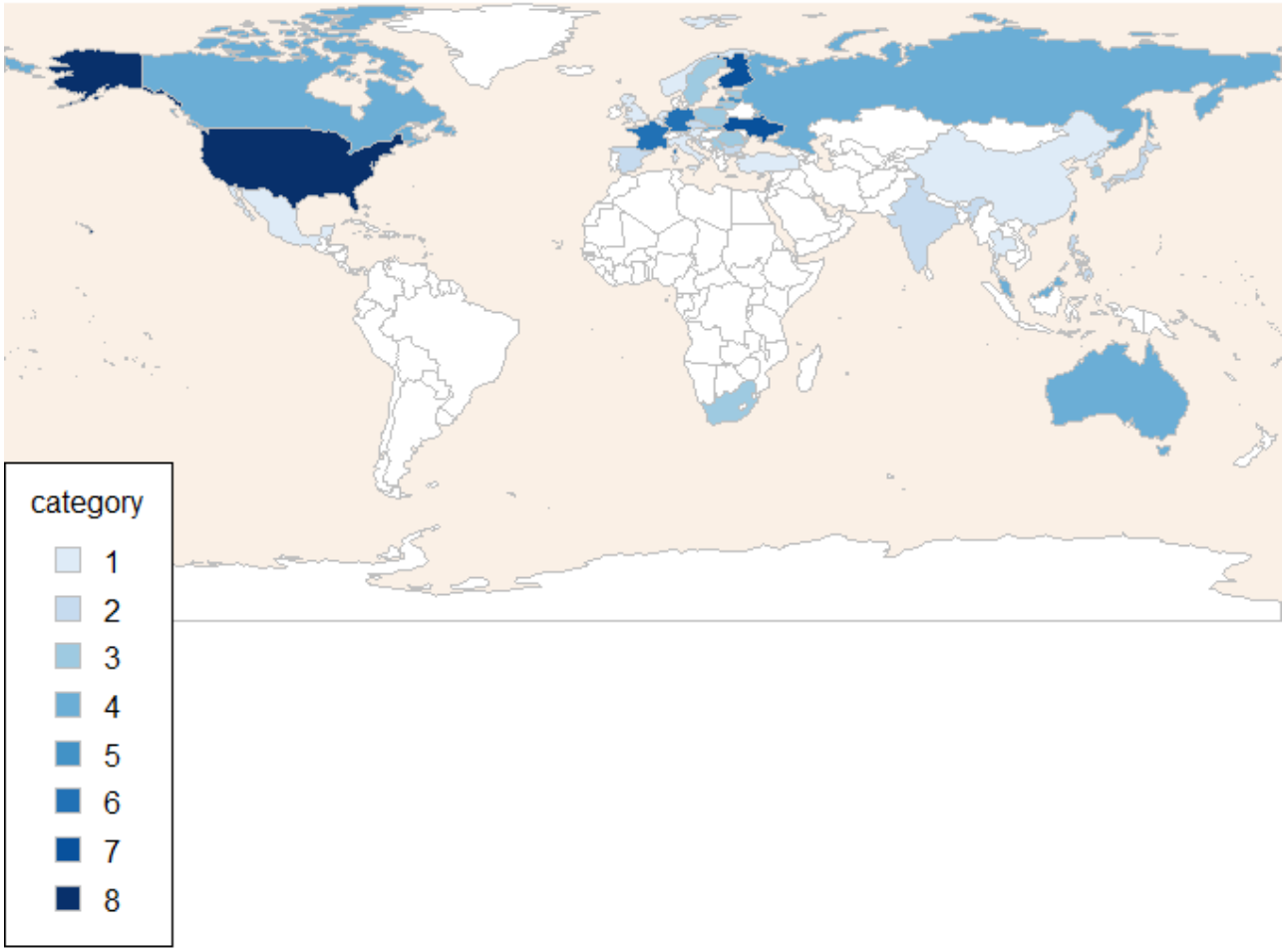
Sample sizes

Overall, the studies included 7746 participants. Of these, 4134 were randomised to vortioxetine. Of the remaining 3612 participants, 2299 were randomised to placebo, 1313 to SNRIs (344 to venlafaxine and 969 to duloxetine). The mean sample size per arm was 209 participants (range 105 to 448).

Setting

All studies were multicentre trials. Six studies were conducted in a single nation: the USA (Jacobsen 2015; Jain 2013; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015c) and Japan (Takeda 2011). One multinational study recruited Asian participants only (Wang 2015). The other studies were multinational across continents. An overview of countries where participants were recruited is given in Figure 2.

Figure 2. Countries participating in trials. The categories represent the number of studies randomising participants within a country.



Four studies enrolled both inpatients and outpatients (Baldwin 2012; Boulenger 2014; McIntyre 2014; Wang 2015). Three studies recruited exclusively outpatients (Alvarez 2012; Jacobsen 2015; Jain 2013). Eight studies did not explicitly report the setting (Henigsberg 2012; Katona 2012; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b; Mahableshwarkar 2015c; NCT01255787; Takeda 2011).

Participants

All studies included participants with a diagnosis of MDD. No trial enrolled people with comorbid psychiatric disorders.

Thirteen studies randomised participants from 18 years of age: eight studies recruited participants aged between 18 and 75 years (Baldwin 2012; Boulenger 2014; Henigsberg 2012; Jacobsen 2015; Jain 2013; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015c), and four studies recruited between the ages of 18 and 65 years (Alvarez 2012; Mahableshwarkar 2015b; McIntyre 2014; Wang 2015). Two studies recruited participants from 20 years of age: one study between the ages of 20 and 64 years (NCT01255787), and one study between the ages of 20 and 75 years (Takeda 2011). One study included only older participants (Katona 2012; aged 65 to 88 years).

Interventions and comparators

Eight studies compared vortioxetine to SNRIs: two compared vortioxetine to venlafaxine (Alvarez 2012; Wang 2015), and six compared vortioxetine to duloxetine (Baldwin 2012; Boulenger 2014; Katona 2012; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b). Seven studies compared vortioxetine to placebo only (Henigsberg 2012; Jacobsen 2015; Jain 2013; McIntyre 2014; Mahableshwarkar 2015c; NCT01255787; Takeda 2011). We found no studies comparing vortioxetine to TCAs/heterocyclics, SSRIs, MAOIs or other antidepressant agents.

One study used a flexible vortioxetine dose scheme (range from 10 mg/day to 20 mg/day) (Mahableshwarkar 2015b). The other 14 trials used a fixed vortioxetine doses scheme (5 mg/day, 10 mg/day, 15 mg/day or 20 mg/day). Two studies applied subtherapeutic dosages of vortioxetine below 5 mg/day (1 mg/day (Henigsberg 2012); 2.5 mg/day (Mahableshwarkar 2013)). These treatment arms were excluded.

Outcomes

All 15 studies provided efficacy data (either as dichotomous or as continuous outcome) and tolerability/acceptability data and could be entered into a meta-analysis.

Nine studies used the MADRS for their primary outcome measures (Alvarez 2012; Baldwin 2012; Boulenger 2014; Jacobsen 2015; Mahableshwarkar 2015a; Mahableshwarkar 2015c; NCT01255787; Takeda 2011; Wang 2015). Four studies used the HAM-D-24 (Henigsberg 2012; Jain 2013; Katona 2012; Mahableshwarkar 2013), two studies used the Digit Symbol Substitution Test (DSST) (Mahableshwarkar 2015b; McIntyre 2014), and one study additionally the Rey Auditory Verbal Learning Test (RAVLT) (McIntyre 2014) for primary outcome measures. For secondary outcomes, the studies used mainly MADRS, CGI-I, Sheehan Disability Scale (SDS), CGI-S, HAM-D-24, and Hamilton Anxiety Rating Scale (HAM-A). Two studies also used the HAM-D-17 (Henigsberg 2012; Takeda 2011), and two studies used additional cognitive tests (DSST, RAVLT, Trail Making Test - A (TMT-A), Trail Making Test - B (TMT-B), Stroop, Perceived Deficits Questionnaire (PDQ), Simple Reaction Time (SRT), Cognitive Reflection Test (CRT), Groton Maze Learning Test (GMLT), Detection Task (DT), Identification Task (IT), and One-Back Task (Mahableshwarkar 2015b; McIntyre 2014)). All studies reported response rates and remission rates. Thirteen studies defined the response rate as 50% or greater decrease from baseline in MADRS total score and two studies as 50% or greater decrease from baseline in HAM-D-24 total score (Jain 2013; Mahableshwarkar 2013). All studies defined the remission rate as MADRS total score of 10 or less.

All studies reported dropouts due to any reason and dropouts due to adverse effects. All but one study (McIntyre 2014) reported dropouts due to inefficacy and the total number of participants who experienced adverse effects.

As expected, the reporting of the individual adverse effects varied markedly. Seven studies reported adverse events if the incidence was at least 5% per arm (Alvarez 2012; Baldwin 2012; Boulenger 2014; Katona 2012; Mahableshwarkar 2015b; McIntyre 2014; Wang 2015). Another seven studies set the threshold at 2% (Henigsberg 2012; Jacobsen 2015; Jain 2013; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015c; NCT01255787), and one study set the threshold at 0% (Takeda 2011).

Excluded studies

Overall, we excluded six studies (14 references) from the systematic review because they did not meet the inclusion criteria. They were designed as relapse prevention studies (Boulenger 2012; NCT02371980), were not conducted in acute therapy (Jacobsen 2015a; Jacobsen 2015b), recruited randomised remitted participants or healthy controls (Browning 2014), or included participants with a treatment-resistant depression (Montgomery 2014) (see Figure 1 and Characteristics of excluded studies table).

Studies awaiting classification

Two studies have recently been completed, but have not yet published results (NCT02272517; NCT02279966). Both studies are short-term randomised, double-blind trials of eight weeks' duration, which examine the effects of vortioxetine on cognitive functions in people with depression in comparison to an SSRI (see Characteristics of studies awaiting classification table).

Ongoing studies

We identified two ongoing studies (see Characteristics of ongoing studies table). The ongoing studies are short-term randomised, double-blind trials of eight weeks' duration (NCT02389816) or 12 weeks' duration (NCT02294305). One study examines the efficacy of vortioxetine for the treatment of depression in people with comorbid social anxiety disorder (NCT02294305). The other study is comparing the efficacy of vortioxetine for the treatment of depression in Japanese people (NCT02389816). One study is ongoing, but not recruiting (NCT02294305), the other is currently recruiting participants (NCT02389816).

Risk of bias in included studies

For graphical representations of the judgements of risk of bias, refer to Figure 3 and Figure 4. Full details of judgements for every included study are presented in the 'Risk of bias' tables within the Characteristics of included studies table.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

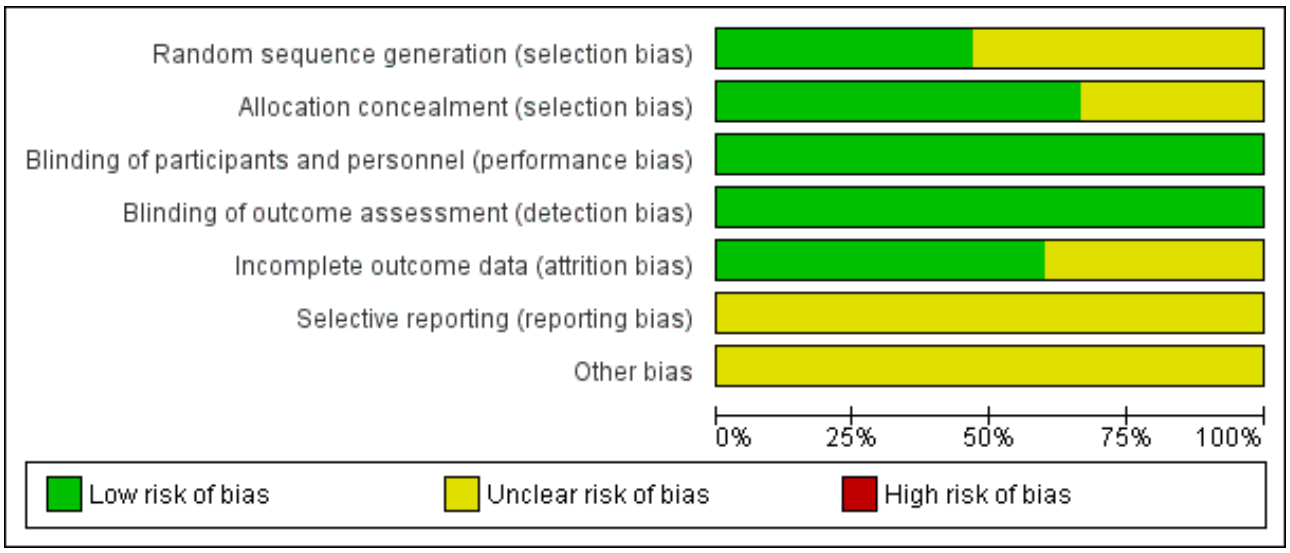
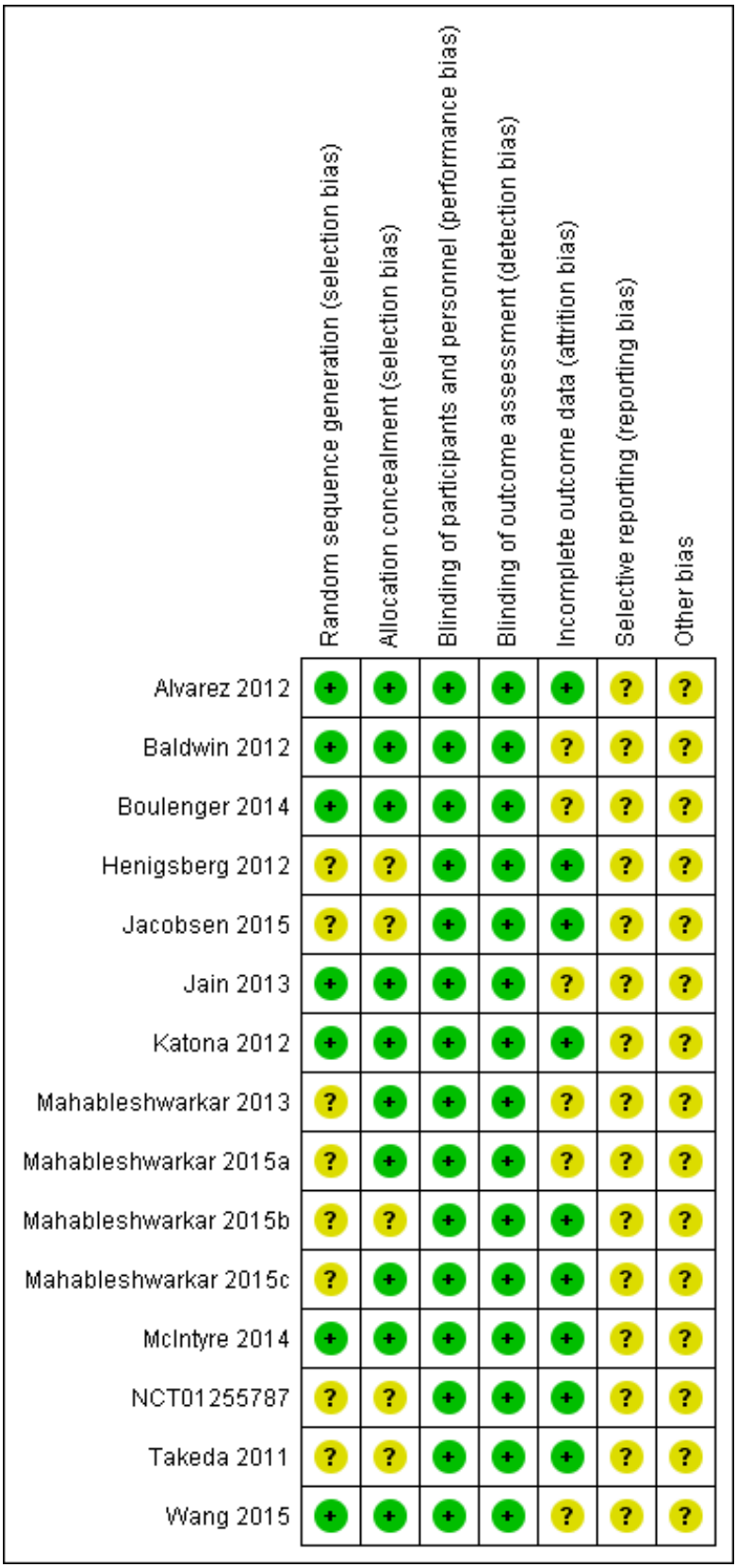


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We rated none of the studies as having a high risk of bias in any domain, but we rated all studies at unclear risk of bias in at least two domains (see Figure 3 and Figure 4 for summary graphs). All studies were sponsored by the pharmaceutical companies that manufactures vortioxetine (Lundbeck, Takeda), and two of them were unpublished.

Allocation

Eight studies did not report details on sequence generation and were judged at unclear risk of bias (Henigsberg 2012; Jacobsen 2015; Mahableshwarkar 2013; Mahableshwarkar 2015a; Mahableshwarkar 2015b; Mahableshwarkar 2015c; NCT01255787; Takeda 2011). In addition, five studies did not adequately describe allocation concealment (Henigsberg 2012; Jacobsen 2015; Mahableshwarkar 2015b; NCT01255787; Takeda 2011).

Blinding

All RCTs were reported as double-blind and so were at low risk of bias. All studies used at least identically appearing capsules for blinding.

Incomplete outcome data

Nine studies had a dropout rate below 20% in all treatment arms and so were at low risk of attrition bias (Alvarez 2012; Henigsberg 2012; Jacobsen 2015; Katona 2012; Mahableshwarkar 2015b; Mahableshwarkar 2015c; McIntyre 2014; NCT01255787; Takeda 2011). Of the six remaining studies, two studies had a dropout rate above 20% in the vortioxetine arm (Baldwin 2012; Boulenger 2014), one study in the active control arm (Wang 2015), one study in the placebo arm (Jain 2013), one study in the vortioxetine and in the active control arm (Mahableshwarkar 2015a), and one study in all arms (Mahableshwarkar 2013). The range in these six studies was from 20.1% to 27.4%. These studies were at unclear risk of attrition bias.

Selective reporting

We rated all included studies at unclear risk of selective reporting bias, because published protocols were unavailable. However, publications and entries in clinical trial registers did not reveal discrepancies.

Other potential sources of bias

All studies were sponsored by the pharmaceutical companies that manufactures vortioxetine (Lundbeck, Takeda) and were, therefore, assessed as having an unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Vortioxetine compared to Placebo for adults with Major Depressive Disorder; **Summary of findings 2** Vortioxetine compared to SNRIs for adults with Major Depressive Disorder

We have reported the results of the present systematic review by grouping the comparators into two classes: placebo and SNRIs. Specific comparators are presented in subgroups where possible. We could not identify relevant studies comparing vortioxetine with TCAs, heterocyclics, SSRIs, MAOIs or other antidepressants.

Comparison 1. Vortioxetine versus placebo

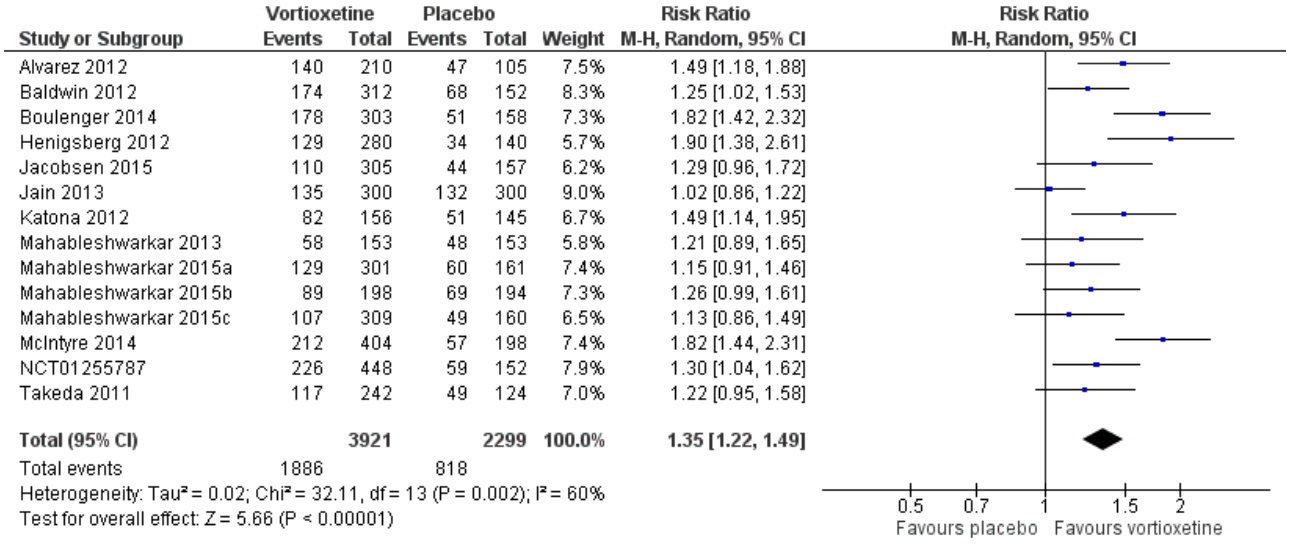
Fourteen studies including 6220 participants contributed data to the comparison of vortioxetine versus placebo (see Summary of findings for the main comparison). The quality of evidence contributing to all outcomes was rated as moderate to very low, because of high dropout rates and statistical heterogeneity.

Primary outcomes

1.1. Response to treatment

There was evidence that vortioxetine was more effective than placebo (Mantel-Haenszel RR 1.35, 95% CI 1.22 to 1.49; P < 0.001; 14 studies, 6220 participants). Statistical heterogeneity was substantial between studies (I^2 = 60%) (Analysis 1.1; Figure 5).

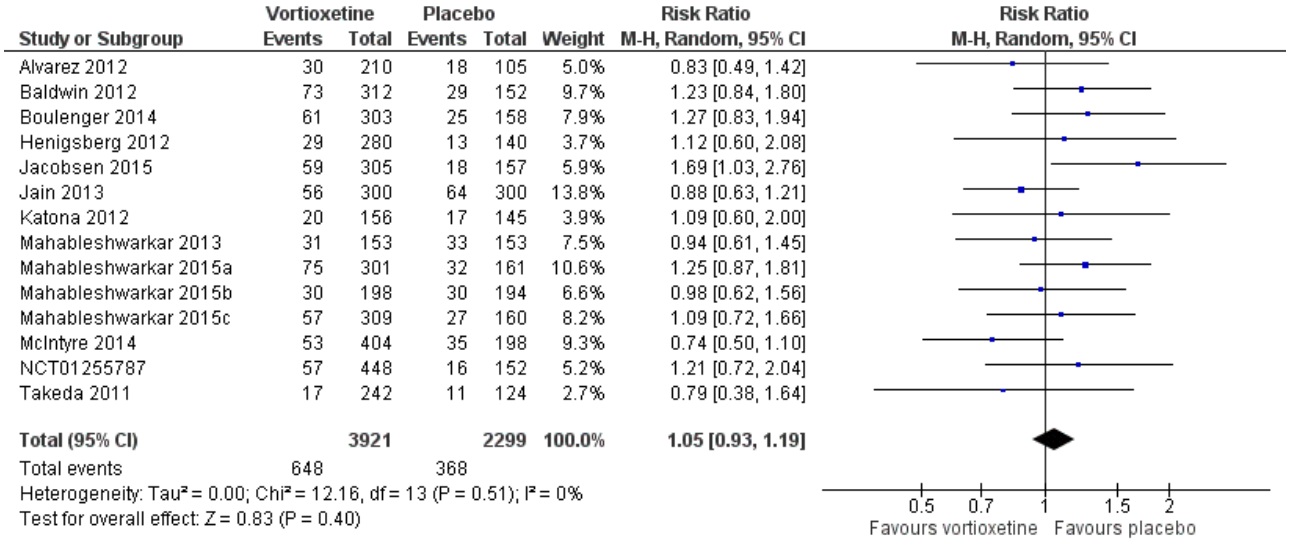
Figure 5. Forest plot of comparison: 1 Vortioxetine versus placebo, outcome: 1.1 Response.



1.2. Total number of dropouts

There was no evidence that vortioxetine was associated with a lower or higher total dropout rate than placebo (RR 1.05, 95% CI 0.93 to 1.19; P = 0.40; 14 studies, 6220 participants). There was no heterogeneity (I^2 = 0%) (Analysis 1.2; Figure 6).

Figure 6. Forest plot of comparison: 1 Vortioxetine versus placebo, outcome: 1.2 Total number of dropouts.



Secondary outcomes

1.3. Achieved remission

There was evidence that more participants achieved remission with vortioxetine than with placebo (RR 1.32, 95% CI 1.15 to 1.53; P < 0.001; 14 studies, 6220 participants). Heterogeneity was substantial between studies (I^2 = 58%) (Analysis 1.3).

1.4. Depressive symptoms

There was evidence that vortioxetine was significantly more effective in lowering MADRS score compared to placebo (MD -2.94, 95% CI -4.07 to -1.80, P < 0.001; 14 studies, 5566 participants). Heterogeneity was high between studies (I^2 = 79%) (Analysis 1.4).

1.5. Dropout due to adverse events

There was evidence that vortioxetine was associated with a higher dropout rate due to adverse events compared to placebo (RR 1.41, 95% CI 1.09 to 1.81; P = 0.008; 14 studies, 6220 participants). There was no heterogeneity (I^2 = 0%) (Analysis 1.5).

1.6. Dropout due to inefficacy

There was evidence that vortioxetine was associated with a lower dropout rate due to inefficacy compared to placebo (RR 0.56, 95% CI 0.34 to 0.90; P = 0.02; 14 studies, 6220 participants). Heterogeneity between studies was moderate (I^2 = 41%) (see Analysis 1.6).

1.7. Tolerability

There was evidence that more participants experienced adverse effects when treated with vortioxetine than when treated with placebo (RR 1.12, 95% CI 1.07 to 1.16; P < 0.001; 14 studies, 6182 participants). Heterogeneity between studies was low (I^2 = 8%) (see Analysis 1.7).

Specific adverse effects compared to placebo are reported descriptively in Analysis 1.14. One study reported all adverse effects mentioned (Takeda 2011). Due to the limits of graphs in Review Manager 5 and in line with the majority of studies, we only reported adverse effects with an incidence of 2% or greater in one of the treatment arms for this study. Serious adverse events are reported in Analysis 1.15.

This analysis was not conducted with ITT data according to our conservative approach (see Measures of treatment effect), but with ITT data as reported in the trials.

Comparison 2. Vortioxetine versus serotonin-norepinephrine reuptake inhibitors

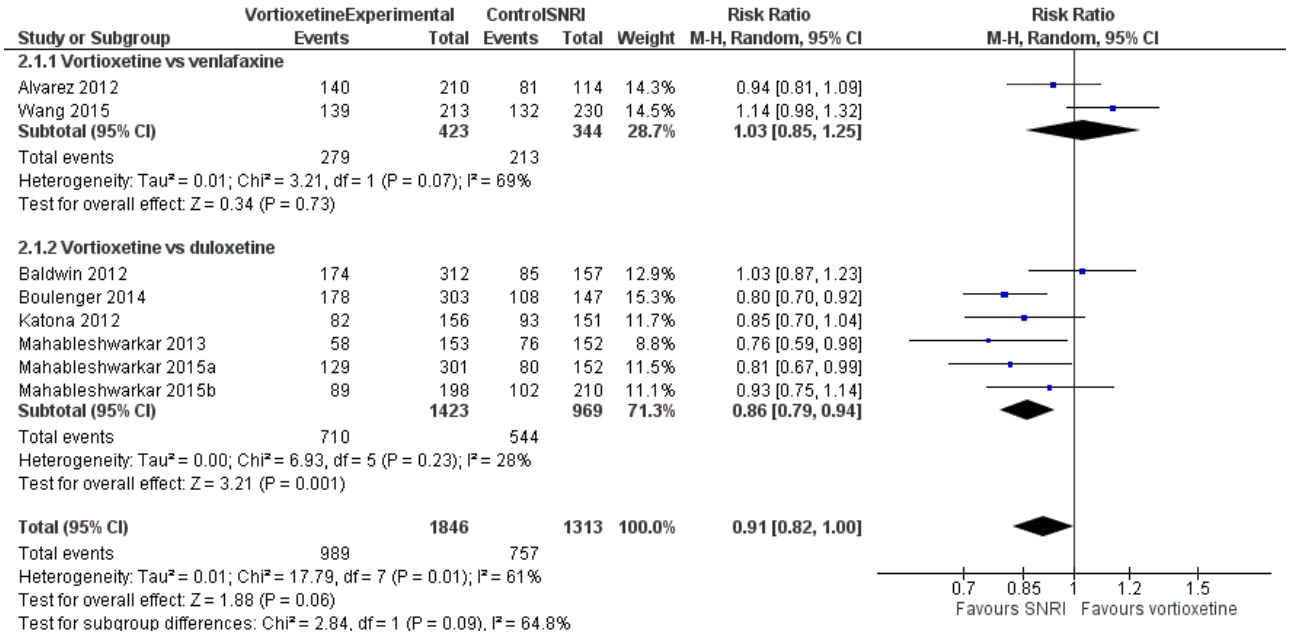
Eight studies including 3159 participants contributed data to the comparison of vortioxetine versus SNRIs (see Summary of findings 2). The quality of evidence contributing to all outcomes was very low because of high dropout rates and substantial statistical heterogeneity.

Primary outcomes

2.1. Response to treatment

There was no evidence that vortioxetine was less or more effective than SNRIs as a whole (RR 0.91, 95% CI 0.82 to 1.00; P = 0.06; 8 studies, 3159 participants). Heterogeneity was substantial between studies (I^2 = 61%) (Analysis 2.1; Figure 7).

Figure 7. Forest plot of comparison: 3. Vortioxetine versus serotonin-norepinephrine reuptake inhibitors, outcome: 3.1 Response.

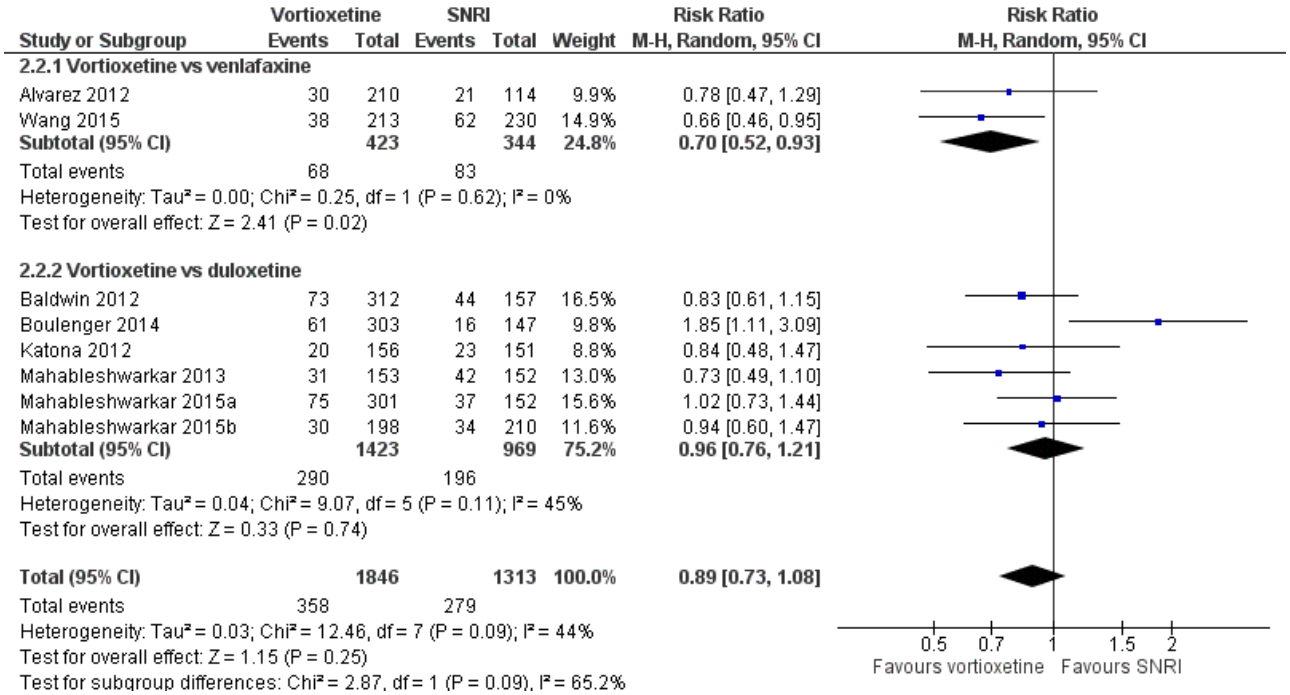


Although there was no statistically significant difference between the specific comparators (Chi^2 = 2.84, degrees of freedom (df) = 1, P = 0.09), response rates were significantly lower for vortioxetine compared to duloxetine (RR 0.86, 95% CI 0.79 to 0.94; P = 0.001; 6 studies, 2392 participants; I^2 = 28%) while there was no difference in response rates compared to venlafaxine (RR 1.03, 95% CI 0.85 to 1.25; P = 0.73; 2 studies, 767 participants; I^2 = 69%).

2.2. Total number of dropouts

There was no evidence that vortioxetine was associated with a lower or higher total dropout rate than SNRIs as a whole (RR 0.89, 95% CI 0.73 to 1.08; P = 0.25; 8 studies, 3159 participants). Heterogeneity between studies was moderate (I^2 = 44%) (Analysis 2.2; Figure 8).

Figure 8. Forest plot of comparison: 3. Vortioxetine versus serotonin-norepinephrine reuptake inhibitors, outcome: 3.2 Total number of dropouts.



There was no significant difference between trials comparing vortioxetine to duloxetine or venlafaxine (Chi^2 = 2.87, df = 1, P = 0.09), but total dropout rates were significantly lower for vortioxetine compared to venlafaxine (RR 0.70, 95% CI 0.52 to 0.93; P = 0.02; 2 studies, 767 participants; I^2 = 0%). There was no statistically significant difference between vortioxetine and duloxetine for total dropouts (RR 0.96, 95% CI 0.76 to 1.21; P = 0.74; 6 studies, 2392 participants; I^2 = 45%).

Secondary outcomes

2.3. Achieved remission

There was no significant difference in the number of participants who achieved remission between vortioxetine and SNRIs as a whole (RR 0.89, 95% CI 0.77 to 1.03; P = 0.11; 8 studies, 3155 participants). Heterogeneity between studies was substantial (I^2 = 57%) (Analysis 2.3).

There was no statistically significant difference between the specific comparators (Chi^2 = 1.15, df = 1, P = 0.28) and there were no statistically significant differences in remission rates between vortioxetine and venlafaxine (RR 0.99, 95% CI 0.81 to 1.20, P = 0.88; 2 studies, 767 participants; I^2 = 37%) or vortioxetine and duloxetine (RR 0.85, 95% CI 0.70 to 1.02; P = 0.09; 6 studies, 2388 participants; I^2 = 58%).

2.4. Depressive symptoms

There was evidence that vortioxetine was less effective in lowering depression scores compared to SNRIs as a whole (MD 1.52, 95% CI 0.50 to 2.53; P = 0.003; 8 studies, 2807 participants). Heterogeneity between studies was moderate (I^2 = 50%) (Analysis 2.4).

There was no significant difference between trials comparing vortioxetine to duloxetine or venlafaxine (Chi^2 = 2.11, df = 1, P = 0.15). Comparing vortioxetine to duloxetine, the depression scores were significantly more reduced by duloxetine (MD 1.99, 95% CI 1.15 to 2.83; P < 0.001; 6 studies, 2106 participants; I^2 = 6%). There was no significant difference for this outcome between vortioxetine and venlafaxine (MD 0.02, 95% CI -2.49 to 2.54; P = 0.99; 2 studies, 701 participants; I^2 = 65%).

2.5. Dropout due to adverse events

There was no evidence that vortioxetine was associated with a lower or higher dropout rate due to adverse events compared to SNRIs as a whole (RR 0.74, 95% CI 0.51 to 1.08; P = 0.12; 8 studies, 3159 participants). Heterogeneity between studies was moderate (I^2 = 55%) (Analysis 2.5).

There was a statistically significant difference between the comparators (Chi^2 = 7.07, df = 1, P = 0.008). Dropout rates due to adverse events were significantly lower for vortioxetine compared to venlafaxine (RR 0.42, 95% CI 0.26 to 0.67; P < 0.001; 2 studies; 767 participants; I^2 = 0%). There was no statistically significant difference between vortioxetine and duloxetine (RR 0.92, 95% CI 0.65 to 1.31; P = 0.65; 6 studies, 2392 participants; I^2 = 30%).

2.6. Dropout due to inefficacy

There was no evidence that vortioxetine was associated with a lower or higher dropout rate due to inefficacy compared to SNRIs as a whole (RR 1.52, 95% CI 0.70 to 3.30; P = 0.29; 8 studies, 3159 participants). Heterogeneity between studies was moderate (I^2 = 30%) (Analysis 2.6).

There was no significant difference between trials comparing vortioxetine to duloxetine or venlafaxine (Chi^2 = 1.29, df = 1, P = 0.26). Furthermore, there were no significant differences in dropout rates due to inefficacy between vortioxetine and venlafaxine (RR 2.68, 95% CI 0.99 to 7.24; P = 0.05; 2 studies, 767 participants; I^2 = 0%) or vortioxetine and duloxetine (RR 1.16, 95% CI 0.41 to 3.31; P = 0.78; 6 studies, 2392 participants; I^2 = 34%).

2.7. Tolerability

There was evidence that fewer participants experienced adverse effects when treated with vortioxetine than when treated with SNRIs as a whole (RR 0.90, 95% CI 0.86 to 0.94; P < 0.001; 8 studies, 3139 participants). There was no heterogeneity (I^2 = 0%) (Analysis 2.7).

There was no statistically significant difference between the specific comparators (Chi^2 = 0.09, df = 1, P = 0.76). The comparison between vortioxetine and duloxetine showed that fewer participants experienced adverse effects when treated with vortioxetine (RR 0.89, 95% CI 0.84 to 0.95; P < 0.001; 6 studies, 2376 participants; I^2 = 18%). There was no significant difference between vortioxetine and venlafaxine (RR 0.91, 95% CI 0.82 to 1.00; P = 0.06; 2 studies, 758 participants; I^2 = 0%).

Specific adverse effects compared to SNRIs are reported descriptively in Analysis 2.16. Specific serious adverse events are reported in Analysis 2.17.

This analysis used ITT data as reported in the trials.

Subgroup analyses

Comparison 1. Vortioxetine versus placebo

Fixed versus flexible dosing schemes

Two studies compared placebo to a flexible dose of vortioxetine (Alvarez 2012; Mahableshwarkar 2015b). There were no significant differences between the subgroups in terms of treatment response (test for subgroup differences: Chi^2 = 0.05, df = 1, P = 0.82; Analysis 1.8) and total number of dropouts (Chi^2 = 0.70, df = 1, P = 0.40; Analysis 1.9).

Treatment setting: primary care versus inpatient care versus outpatient care

We found no studies in primary care settings and all studies including inpatients also included outpatients, so it was impossible to conduct this subgroup analysis.

Older people (aged greater than 65 years): included versus excluded

We excluded four studies from this subgroup analysis, because it was unclear if older participants were included (Henigsberg 2012; Jain 2013; Mahableshwarkar 2013; Takeda 2011). Four studies excluded older participants (Alvarez 2012; Mahableshwarkar 2015b; McIntyre 2014; NCT01255787). One study recruited only older participants (Katona 2012). There were no differences in response rates between the subgroups (Chi^2 = 0.52, df = 1, P =

0.47; Analysis 1.10), but dropout rates differed significantly (Chi^2 = 5.02, df = 1, P = 0.02; Analysis 1.11). In the studies including older participants, the dropout rates were significantly lower in the placebo groups (RR 1.25, 95% CI 1.05 to 1.49; P = 0.01; I^2 = 0%). The number of total dropouts was not significantly different compared to placebo in the studies excluding older participants (RR 0.90, 95% CI 0.71 to 1.13; P = 0.36; I^2 = 0%).

Comparison 2. Vortioxetine versus serotonin-norepinephrine reuptake inhibitors

Fixed versus flexible dosing schemes

One study compared a flexible dose of vortioxetine 10 mg to 20 mg versus a fixed dose of duloxetine 60 mg/day (Mahableshwarkar 2015b). All other studies used a fixed dose scheme. The study with a flexible dose found no significant differences in terms of response rates (Chi^2 = 0.03, df = 1, P = 0.86; Analysis 2.8) and total dropouts (Chi^2 = 0.04, df = 1, P = 0.84; Analysis 2.9), as compared to the fixed-dose studies.

Treatment setting: primary care versus inpatient care versus outpatient care

We found no studies in primary care settings and all studies including inpatients also included outpatients, so it was impossible to conduct this subgroup analysis.

Older participants (aged greater than 65 years): included versus excluded

We excluded one study from this analysis, because it was unclear if older participants were included in the study population (Mahableshwarkar 2013). Three studies comparing vortioxetine to an SNRI excluded older participants (Alvarez 2012; Mahableshwarkar 2015b; Wang 2015). There was no significant difference between the subgroups in response rates (test for subgroup differences: Chi^2 = 2.52, df = 1, P = 0.11; Analysis 2.10) and total dropout rates (test for subgroup differences: Chi^2 = 2.38, df = 1, P = 0.12; Analysis 2.11).

Sensitivity analyses

The following sensitivity analyses were defined a priori.

Exclusion of trials with unequal dosing

This sensitivity analysis is only meaningful for the comparisons of vortioxetine with active comparators.

In six studies, vortioxetine and control antidepressants were compared using unequal doses. Two studies compared vortioxetine 5 mg/day (25% of the maximum dose) to duloxetine 60 mg/day (50% of the maximum dose) (Katona 2012; Mahableshwarkar 2013), and one compared vortioxetine 5 mg/day or 10 mg/day (50% of the maximum dose) to venlafaxine 225 mg/day (100% of the maximum dose for moderately depressed outpatients) (Alvarez 2012). Two studies used higher vortioxetine doses and compared vortioxetine 15 mg/day or 20 mg/day (100% of the maximum dose) to duloxetine 60 mg/day (50% of the maximum dose) (Boulenger 2014; Mahableshwarkar 2015a). One study compared flexible dosing of vortioxetine to a fixed dose of duloxetine (Mahableshwarkar 2015b). To increase the usability of the analysis, the analysis was conducted by grouping the comparisons into subgroups according to the direction of the imbalance in dosing.

The analysis of response rates revealed statistically significant differences between the groups (Chi^2 = 14.99, df = 3, P = 0.002; Analysis 2.12). The two trials with fair (or comparable) dosing found no differences between vortioxetine and SNRIs (RR 1.09, 95% CI 0.97 to 1.22; P = 0.13; 912 participants; I^2 = 0%), but the studies using higher and lower vortioxetine doses than comparator showed significantly higher response rates in participants treated with SNRIs (higher: RR 0.80, 95% CI 0.72 to 0.90; P < 0.001; 2 studies, 903 participants; I^2 = 0%; lower: RR 0.87, 95% CI 0.78 to 0.98; P = 0.02; 3 studies, 936 participants; I^2 = 9%).

The analysis of the total number of dropouts found no statistically significant differences between the subgroups (Chi^2 = 3.68, df = 3, P = 0.30; Analysis 2.13). In the trials with fair (or comparable) dosing, vortioxetine showed statistically significant lower total dropout rate than SNRIs as a whole (RR 0.75, 95% CI 0.59 to 0.96; P = 0.02; 2 studies, 912 participants; I^2 = 0%). The studies using higher vortioxetine doses, lower vortioxetine doses and flexible versus fixed dosing found no statistically significant dropout rates between vortioxetine and SNRIs (higher dose: RR 1.33, 95% CI 0.74 to 2.39; P = 0.33; 2 studies, 903 participants; I^2 = 72%; lower vortioxetine dose: RR 0.77, 95% CI 0.59 to 1.02; P = 0.06; 3 studies, 936 participants; I^2 = 0%; flexible versus fixed dosing: RR 0.94, 95% CI 0.60 to 1.47; P = 0.77; 1 study, 408 participants).

Exclusion of studies that did not employ a double-blind approach

All our included studies were double-blinded.

Exclusion of studies with subsets of participants with bipolar disorders

None of the included studies randomised people with bipolar disorder.

Exclusion of trials with dropout rates of more than 20% in one of the treatment arm included

This sensitivity analyses were performed for the comparisons of vortioxetine with placebo and vortioxetine with SNRIs.

Six studies reported overall dropout rates of more than 20% and were excluded (Baldwin 2012; Boulenger 2014; Jain 2013; Mahableshwarkar 2013; Mahableshwarkar 2015a; Wang 2015).

The analyses of response rates showed no significant differences between dropout rates below and above 20% for the comparison between vortioxetine and placebo (Chi^2 = 1.00, df = 1, P = 0.32; Analysis 1.12) and the comparison between vortioxetine and SNRIs (Chi^2 = 0, df = 1, P = 0.95; Analysis 2.14).

The analyses of the total number of dropouts found no statistically significant differences between the subgroups for the comparison between vortioxetine and placebo (Chi^2 = 0.21, df = 1, P = 0.64; Analysis 1.13) and the comparison between vortioxetine and SNRIs (Chi^2 = 0.11, df = 1, P = 0.74; Analysis 2.15).

Exclusion of studies with imputed data

There is no need for this sensitivity analysis, because the analysis did not include imputed data.

Exclusion of studied sponsored by the manufacturer of vortioxetine

All studies were conducted by the manufacturers of vortioxetine, therefore this sensitivity analysis is not meaningful.

Reporting bias

We examined the funnel plot for the primary outcomes for the comparison of vortioxetine and placebo only, because the comparison with SNRIs did not contain more than 10 studies. Both funnel plots were inconclusive. We were able to identify two unpublished trials (NCT01255787; Takeda 2011).

DISCUSSION

Summary of main results

Our review included 15 studies (7746 participants). Statistically, vortioxetine was more effective than placebo. This advantage was consistent across the three efficacy outcomes of response, remission and depressive symptoms, although the quality of the evidence was low for response and remission and very low for depressive symptoms (see Summary of findings for the main comparison). Clinically, there is uncertainty on the relevance of these differences. According to some authors, statistically significant differences in response and remission rates should be accepted as clinically relevant (Montgomery 2009), but in the present review we estimated a RR of 1.35 for response and 1.32 for remission, which correspond to a number needed to treat for an additional beneficial outcome (NNTB) of 8 (95% CI 5 to 12) for response and 13 (95% CI 8 to 29) for remission (assuming a baseline response and remission rate of 356/1000 for response and 224/1000 for remission; see Summary of findings for the main comparison). Thus, doctors would need to treat 8 (95% CI 5 to 12) people with vortioxetine, rather than placebo, for one additional responding patient and 13 people (95% CI 8 to 29) for one additional remitting patient. Furthermore, the difference in change scores between vortioxetine and placebo was estimated to be fewer than 3 points on the MADRS at study endpoint. Some authors suggested that a difference of 2 points on HAM-D or MADRS is already clinically relevant (Montgomery 2009), but others have shown that an improvement of up to 3 points on the HAM-D-17 corresponded to "no change" on CGI (Leucht 2013). Clearly, this casts uncertainty on the real added value of vortioxetine. We found no statistically significant difference in terms of total dropout rates, although more participants discontinued vortioxetine because of adverse effects, while significantly more participants discontinued placebo because of inefficacy. The subgroup or sensitivity analysis revealed no factors that significantly influenced the results.

In comparison with other antidepressants, very low quality of evidence found no clinically significant advantage in efficacy of vortioxetine over the SNRIs as a class (see Summary of findings 2). Against individual antidepressants, the analyses of response rates and change in depressive symptoms scores suggested that vortioxetine may be less effective than duloxetine, although in terms of remission rates, there was no difference. Against venlafaxine, meta-analysis of two studies found no statistically significant differences. In terms of tolerability, our analyses of total dropout rates and dropouts due to adverse events or inefficacy found no significant differences between vortioxetine and the SNRIs as a class. In terms of number of participants reporting at least one adverse effect, vortioxetine was better than the SNRIs as a class and duloxetine. However, the sensitivity analysis casts some doubts on this result, as only two studies used comparable dosing.

Overall completeness and applicability of evidence

All studies included were conducted in highly selected populations, excluding, for example, people with psychiatric comorbidities and suicidal ideation, which are commonly seen in everyday practice. Thus, the external validity of our results may be limited. Furthermore, we were unable to identify studies that compared vortioxetine to pharmacological classes other than SNRI, which is a major limitation in terms of applicability of the evidence in routine care, as the SSRIs are the most commonly prescribed antidepressants as first-line treatment.

In accordance with the protocol, we did not conduct meta-analysis on adverse events and did not include scales assessing accompanying symptoms, although these aspects may be of paramount relevance in clinical practice, often guiding the selection of an antidepressant (Gartlehner 2012). Our list of adverse events shows that there is considerable variance in naming, grouping and reporting adverse events; similarly, functional outcomes or accompanying symptoms were erratically assessed and reported. Thus, meta-analyses of these outcomes cannot be informative and may rather be misleading in informing clinical practice.

Quality of the evidence

We chose seven outcomes for assessing the quality of evidence and to construct the 'Summary of findings' tables (the chosen outcomes being: response, total number of dropouts, remission, depressive symptoms, dropouts due to adverse events, dropouts due to inefficacy, tolerability expressed as patient experiencing as least one adverse event). We constructed two separate 'Summary of findings' tables: one for vortioxetine compared to placebo (Summary of findings for the main comparison), and one for vortioxetine compared to SNRIs (Summary of findings 2).

The quality of the evidence for the comparisons of vortioxetine and placebo was low for remission and response rates and very low for the analysis of depressive symptoms, showing uncertainty in the magnitude of effect. The quality was downgraded because of high dropout rates in some of the trials or because of statistical heterogeneity. We rated the quality of the evidence with respect to treatment discontinuation as moderate for all three outcomes in studies of vortioxetine versus placebo (Summary of findings for the main comparison).

For studies comparing vortioxetine versus the SNRIs, the quality of the evidence was very low for all outcomes (Summary of findings 2). The quality was downgraded because of high dropout rates and substantial statistical heterogeneity.

Study limitations (risk of bias)

All studies employed proper double-blind procedures and adequate masking of the outcome assessment. However, we judged that all outcomes in studies comparing vortioxetine versus placebo had a serious risk of bias, as about 30% of studies showed an overall dropout rate above 20%. We downgraded the quality of evidence by one level accordingly. In studies comparing vortioxetine versus the SNRIs, the risk of bias was very serious for all outcomes, as about 60% of studies had a dropout rate above 20%.

Consistency of effect

In studies comparing vortioxetine versus placebo, there was a moderate degree of heterogeneity (I^2 = 30% to 60%) (Schünemann 2013) for the outcomes 'response' and 'remission.' The quality of evidence was downgraded by one level. There was a substantial degree of heterogeneity (I^2 = 60% to 90%) for the outcome 'depressive symptoms.' For this reason, we downgraded the quality of evidence by two levels for these outcomes. In the comparison vortioxetine versus SNRIs, there was a moderate degree of heterogeneity for four outcomes, namely 'response,' 'remission,' 'depressive symptoms' and 'dropouts due to adverse events.' We downgraded the quality of evidence by one level. Reasons underpinning this statistical heterogeneity are uncertain. In general, included studies were homogeneous in terms of clinical features of participants, as the vast majority enrolled participants with the same diagnosis and within the same range of age. Also trial duration was very similar between studies, while the characteristics of the setting differed between studies (see Included studies).

Indirectness

We judged that there was no serious risk of indirectness, as the diagnostic criteria, the characteristics of participants, type of interventions and outcomes largely matched those of interest. Most studies were conducted in high- and middle-income countries, especially in the US. Evidence for people from large parts of the world, for example, Africa, South America and the Middle East was lacking (see Figure 2).

Imprecision

For studies comparing vortioxetine versus placebo, there was no serious risk of imprecision, because of the relatively large number of participants and events. However, for studies comparing vortioxetine versus SNRIs, we downgraded the outcomes 'total dropouts' and 'dropouts due to adverse events' by one level for serious risk of imprecision, as the 95% CI crossed both 1 (no differences) and 0.75 (appreciable benefit for vortioxetine) (according to Guyatt 2011). The outcome 'dropouts due to inefficacy' was downgraded by two levels for very serious risk of imprecision, as the 95% CI crossed 1 (no differences), 0.75 (appreciable benefit for vortioxetine) and 1.25 (appreciable benefit for SNRIs).

Publication bias

Visual inspection of the funnel plot did not suggest a relevant risk of publication bias. Our review included some unpublished studies and this may have reduced the impact of publication bias. As experts in the field were contacted during the search phase, it is unlikely that relevant studies were overlooked. However, although the search was thorough, there is still the possibility of not having identified unpublished studies, considering that standardised procedures to perform this type of search are lacking (Chan 2012), and that all studies were sponsored by the pharmaceutical company.

Potential biases in the review process

Although we judged our funnel plots to be inconclusive and we cannot rule out that we missed studies, we consider that our study sample is rather comprehensive and less prone to publication bias in comparison to, for example, reviews of agomelatine (Guaiana 2013; Koesters 2013). We included two unpublished trials only, but, for example, the failed trial and the three negative trials listed in the FDA medical review (CDER 2013) have been published and are included in our review (Baldwin 2012; Jain 2013; Mahableshwarkar 2013; Mahableshwarkar 2015c). However, there is some evidence for a sponsorship bias in antidepressant research favouring the experimental drug (Barbui 2004; Weinmann 2008). Our analysis contained only trials conducted by the manufacturers, so we cannot rule out a sponsorship bias in favour of vortioxetine in our data. Furthermore, our analysis combined different doses of vortioxetine, which may have increased heterogeneity of the effects. However, considering that previous reviews found no significant dose-response effects (Meeker 2015; Thase 2016), this approach may be justified. Furthermore, doses may also vary considerably across participants within study arms and it therefore may be necessary to review these effects based on individual participant data.

Agreements and disagreements with other studies or reviews

Our review is in line with previous reviews of vortioxetine (e.g. Meeker 2015; Thase 2016; Zhang 2015) showing that vortioxetine has a statistically significant advantage compared to placebo in terms of efficacy, but did not show an advantage compared to SNRIs. However, considering the quality of the evidence and other potential sources of bias, we suggest caution in the interpretation of efficacy data. This cautious interpretation is in line with findings from previous reviews, for example by not finding a clear dose-response relationship (Meeker 2015; Thase 2016), and the noteworthy finding that only high doses (20 mg/day) of vortioxetine were significantly superior to placebo in US populations (Thase 2016; Zhang 2015). Furthermore, the findings that duloxetine was more effective than vortioxetine, and that there was no difference in terms of efficacy between vortioxetine and venlafaxine, are inconsistent with the evidence showing the superior efficacy of venlafaxine over duloxetine (Cipriani 2009; Schueler 2011). We are aware of the limitations of such an indirect comparison, but these inconsistencies raise some questions about the validity of the findings.

AUTHORS' CONCLUSIONS

Implications for practice

The place of vortioxetine in the treatment of acute depression is unclear. Our analysis showed vortioxetine to be more effective than placebo in terms of response, remission and depressive symptoms, but the clinical relevance of these effects is uncertain, because of the small magnitude of effect, the poor quality of evidence and the highly selected participants enrolled In comparison to serotonin-norepinephrine reuptake inhibitor (SNRI), there was no advantage for vortioxetine, and no studies compared vortioxetine with any of the selective serotonin reuptake inhibitor (SSRIs). Therefore, the available data leave uncertainty on whether vortioxetine is similarly effective, more effective or even less effective in comparison with these reference antidepressants. Vortioxetine might be less effective than duloxetine, but may have advantages over the SNRIs in terms of tolerability profile, as fewer participants reported adverse effects when treated with vortioxetine compared to SNRIs. According to the US Food and Drug Administration (FDA), the adverse effect profile might be similar to that of the SSRIs (Zhang 2015).

Implications for research

A major limitation of the current evidence is the lack of comparisons with the SSRIs, which are usually recommended as first-line treatments for acute depression. Therefore, direct comparisons to these agents may help better determine the place of vortioxetine in the treatment of depression. Two studies that compared vortioxetine to an SSRI have recently been completed and may cushion the limitations, although both trials focus on the effects on cognition (see Studies awaiting classification). Future studies should also address and report adverse effects of competitive treatment options using more standardised approaches, to ascertain if vortioxetine is better tolerated than other antidepressants. Furthermore, advanced meta-analytical approaches, such as individual participant data meta-analyses should be conducted to investigate whether a dose-response effect exists, and whether efficacy is moderated by trial characteristics, including countries and settings, a challenging issue which received little attention so far (Zhang 2015). The paucity of direct head-to-head comparisons between vortioxetine and other antidepressants would suggest a requirement for multiple-treatment meta-analyses attempting to address how this new antidepressant compares, in terms of efficacy and tolerability, with SSRIs.

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Other contributions

We thank Sarah Dawson (CCMD Trials Search Co-ordinator) for developing and writing the search strategy and Sabine Reiser for help with the data management and for additional data checks.

The CCMD Group produces standard text for use in the Methods section of their reviews. We have used this text and adapted it as required.

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Disclaimer

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alvarez 2012

Methods	**Study design:** double-blind, randomised, placebo-controlled, active reference study.
Participants	**Diagnosis:** MDE as primary diagnosis according to DSM-IV-TR criteria; current MDE duration ≥ 3 months and < 12 months; MADRS total score ≥ 30. **Method of diagnosis:** MINI. **Age:** 18-65 years. **Sex:** 63% women. **Location:** multinational (Australia, Austria, Canada, Czech Republic, Finland, France, Italy, Malaysia, Slovakia, Spain, Sweden). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal behaviour therapy or systematic psychotherapy excluded. **Adjunctive medication:** occasional use of zolpidem, zopiclone and zaleplon for insomnia allowed. **Sample size:** vortioxetine 5 mg/d: 109; vortioxetine 10 mg/d: 101; venlafaxine: 114; placebo: 105.
Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 5 mg/day; • vortioxetine 10 mg/day;

Alvarez 2012 *(Continued)*

- venlafaxine XL 75-225 mg/day;
- placebo.

6-week double-blind treatment period. Randomised participants were given 1-week wallet cards at each visit and were instructed to take 2 capsules per day, orally, at the same time every day (preferably in the morning). Efficacy and tolerability assessed at screening, baseline, and after 1, 2, 3, 4, 5 and 6 weeks. Participants who completed the 6-week double-blind period entered a 2-week double-blind taper period.

Outcomes	**Time points for assessment:** 1, 2, 3, 4, 5 and 6 weeks' treatment and 4 weeks' follow-up. **Primary outcome:** • change from baseline in MADRS total score after 6 weeks' treatment. **Secondary outcomes:** • change from baseline in MADRS total score after 1 week of treatment; • change from baseline in HAM-D-24 total score after 6 weeks of treatment; • change from baseline in HAM-A total score after 6 weeks of treatment; • change from baseline in CGI-S score after 6 weeks of treatment; • change in clinical status using CGI-I score at week 6; • proportion of responders at week 6; • proportion of remitters at week 6.
Notes	**Date of study:** 2006-2007. **Funding source:** H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients who met the selection criteria at the baseline visit were assigned to double-blind treatment according to a computer-generated randomisation."
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All investigators, study personnel and participants were blinded to treatment assignment for the duration of the entire study. The randomisation code was broken for one patient (accidentally) who had completed the study before this was discovered, and was therefore not withdrawn from the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal dropout rates < 20%; ITT analyses used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Baldwin 2012

Methods	**Study design:** randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study.
Participants	**Diagnosis:** MDE as primary diagnosis according to DSM-IV-TR criteria; moderate-to-severe depression; current MDE duration ≥ 3 months; MADRS total score ≥ 26. **Method of diagnosis:** MINI. **Age:** range 18-74 years. **Sex:** 68% women. **Location:** multinational (Australia, Bulgaria, Canada, the Czech Republic, Estonia, Finland, France, Hong Kong, India, Republic of Korea, Latvia, Lithuania, Malaysia, Philippines, Romania, Slovakia, Spain, Taiwan, Turkey and Ukraine). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal psychological treatment excluded. **Adjunctive medication:** occasional use of zolpidem, zopiclone and zaleplon for severe insomnia allowed (maximum 2 days/week, not the night before a study visit). **Sample size:** vortioxetine 2.5 mg/d: 155; vortioxetine 5 mg/d: 159; vortioxetine 10 mg/d: 153 ; duloxetine: 157; placebo: 152. **Setting:** inpatients and outpatients.
Interventions	Participants were randomly assigned to 1 of 5 treatments: • vortioxetine 2.5 mg/day; • vortioxetine 5 mg/day; • vortioxetine 10 mg/day; • duloxetine 60 mg/day; • placebo. 8-week double-blind treatment period. Efficacy and tolerability assessed at screening, baseline, and after 1, 2, 4, 6 and 8 weeks. Participants who completed the 8-week double-blind period could continue in a 52-week open-label, flexible-dose extension study. Study medication given as capsules of identical appearance. Randomised participants instructed to take 1 capsule per day, orally, at the same time every day (preferably in the morning).
Outcomes	**Time points for assessment:** 1, 2, 4, 6 and 8 weeks' treatment and 4 weeks' follow-up. **Primary outcome:** • change from baseline in MADRS total score after 8 weeks of treatment. **Secondary outcomes:** • change from baseline in HAM-D-24 total score after 8 weeks of treatment; • proportion of responders at week 8; • change in clinical status using CGI-I score at week 8; • change from baseline in HAM-D-24 total score after 8 weeks of treatment in participants with baseline HAM-A total score ≥ 20; • change from baseline in SDS total score after 8 weeks of treatment; • proportion of remitters at week 8; • change from baseline in HAM-A total score after 8 weeks of treatment; • change from baseline in CGI-S score after 8 weeks of treatment;

Baldwin 2012 *(Continued)*

- change from baseline in ASEX total score after 8 weeks of treatment.

Notes	**Date of study:** 2008-2009. **Funding source:** H. Lundbeck A/S. Participants not participating in the continuation study entered a 1-week, double-blind taper period, during which those on placebo remained on placebo; participants taking vortioxetine 2.5 mg/day, 5 mg/day or 10 mg/day switched abruptly to placebo and participants taking duloxetine 60 mg/day received duloxetine 30 mg/day. The same regimen was offered to participants who withdrew from the study before completion of the acute treatment period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...a computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	Central randomisation. Quote: "The details of the randomisation series were unknown to investigators and contained in a set of sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All investigators, trial personnel and patients were blinded..." "capsules of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate > 20% in the vortioxetine arm.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Boulenger 2014

Methods	**Study design:** double-blind, randomised, fixed-dose, placebo-controlled, active-referenced study.
Participants	**Diagnosis:** recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x); current episode of MDE > 3 months; MADRS total score ≥ 26; CGI-S score ≥ 4. **Method of diagnosis:** MINI. **Age:** range 18-75 years. **Sex:** 66% women. **Location:** multinational (Belgium, Estonia, Finland, France, Germany, Latvia, Lithuania, Norway, Russia, Slovakia, South Africa, Sweden and Ukraine).

Boulenger 2014 *(Continued)*

	Comorbidities: none. **Adjunctive therapy:** people receiving formal psychological treatment excluded. **Adjunctive medication:** occasional use of zolpidem, zopiclone and zaleplon for severe insomnia allowed (maximum 2 days/week, not the night before a study visit). **Sample size:** vortioxetine 15 mg/d: 152; vortioxetine 20 mg/d: 151; duloxetine: 147; placebo: 158. **Setting:** inpatients and outpatients.
Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 15 mg/day; • vortioxetine 20 mg/day; • duloxetine 60 mg/day; • placebo. 8-week double-blind treatment period. Participants in vortioxetine group received vortioxetine 10 mg/day in week 1 and 15 mg/day or 20 mg/day in weeks 2-8. Participants in duloxetine group received duloxetine 30 mg/day in week 1 and 60 mg/day in weeks 2-8. Participants seen weekly during the first 2 weeks of treatment and then every 2 weeks. Study medication given as capsules of identical appearance. Following randomisation, participants instructed to take 1 capsule per day, orally, preferably in the morning.
Outcomes	**Time points for assessment:** pre- and post-treatment and follow-up 4 weeks after completion or after withdrawal. **Primary outcome:** • change from baseline in MADRS total score after 8 weeks of treatment. **Secondary outcomes:** • proportion of responders at week 8; • change in clinical status using CGI-I score at week 8; • change from baseline in MADRS total score after 8 weeks of treatment in people with baseline HAM-A total score ≥ 20; • proportion of remitters at week 8; • change from baseline in SDS total score after 8 weeks of treatment; • change from baseline in ASEX total score after 8 weeks of treatment; • potential discontinuation symptoms after abrupt discontinuation of treatment with vortioxetine.
Notes	**Date of study:** 2010-2011. **Funding source:** H. Lundbeck A/S. Participants who withdrew were seen for a withdrawal visit as soon as possible and were offered a down-taper regimen. Those who completed the 8-week, double-blind treatment period entered a 2-week, double-blind discontinuation period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were assigned to double-blind treatment according to a randomisation list that was computer generated by H. Lundbeck A/S."
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were contained in a set of sealed opaque envelopes."

Boulenger 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All investigators, trial personnel and patients were blinded to treatment assignment [...]. The randomisation code was not broken for any patient during the study" "capsules of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate > 20% in the vortioxetine arm.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Henigsberg 2012

Methods	**Study design:** multicentre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.
Participants	**Diagnosis:** primary diagnosis of MDE according to DSM-IV-TR criteria; current MDE ≥ 3 months; MADRS total score ≥ 26. **Method of diagnosis:** MINI. **Age:** range 18-75 years. **Sex:** 61% women. **Location:** multinational (Australia, Croatia, France, Germany, Latvia, Lithuania, Malaysia, Netherlands, Poland, Republic of Korea, Russia, South Africa, Taiwan and Ukraine). **Comorbidities:** none. **Adjunctive therapy:** not reported. **Adjunctive medication:** not reported. **Sample size:** vortioxetine 1 mg/d: 140; vortioxetine 5 mg/d: 140; vortioxetine: 10 mg/d: 140; placebo: 140. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 1 mg/day; • vortioxetine 5 mg/day; • vortioxetine 10 mg/day; • placebo. 8-week, double-blind treatment period. All study medication identical in appearance and dispensed using unique identification numbers. Participants returned to study site for assessments at baseline and weeks 1, 2, 4, 6 and 8.
Outcomes	**Time points for assessment:** 1, 2, 4, 6 and 8 weeks' treatment and 4 weeks' follow-up.

Henigsberg 2012 *(Continued)*

Primary outcome:

- change from baseline in HAM-D-24 total score at week 8.

Secondary outcomes:

- change from baseline in SDS total score at week 8;
- clinical CGS-I at week 8;
- % responders in HAM-D-24 total score at week 8;
- change from baseline in HAM-D-24 total score at week 8 in participants with baseline HAM-A score ≥ 20;
- % participants in MADRS remission at week 8;
- change from baseline in HAM-D-24 total score at other weeks assessed;
- change from baseline in SDS total score at other weeks assessed;
- CGI-I at other weeks assessed;
- % responders in HAM-D-24 total score at other weeks assessed;
- change from baseline in HAM-D-24 total score at other weeks assessed in participants with a baseline HAM-A score ≥ 20;
- % participants in MADRS remission at other weeks assessed;
- % participants with a sustained response in HAM-D-24 total score;
- change from baseline in MADRS total score at each week assessed;
- change from baseline in HAM-A total score at each week assessed;
- change from baseline in CGI-S of Illness at each week assessed;
- change from baseline in HAD scales at each week assessed;
- change from baseline in SF-36 Physical Functioning subscore at all weeks assessed;
- change from baseline in SF-36 Role - Physical subscore at all weeks assessed;
- change from baseline in SF-36 Bodily Pain subscore at all weeks assessed;
- change from baseline in SF-36 General Health subscore at all weeks assessed;
- change from baseline in SF-36 Vitality subscore at all weeks assessed;
- change from baseline in SF-36 Social Functioning subscore at other weeks assessed;
- change from baseline in SF-36 Role - Emotional subscore at all weeks assessed;
- change from baseline in SF-36 Mental Health subscore at all weeks assessed;
- healthcare resource utilisation as assessed by the Health Economic Assessment Questionnaire.

Notes	**Date of study:** August 2008 to August 2009. **Funding source:** Takeda; H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned;" no details reported.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study medication was identical in appearance and dispensed using unique identification numbers."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.

Henigsberg 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and equal dropout rates; ITT analyses used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Jacobsen 2015

Methods	**Study design:** phase 3, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.
Participants	**Diagnosis:** recurrent MDE as primary diagnosis according to the American Psychiatric Association Diagnostic and DSM-IV-TR criteria; MADRS total score ≥ 26 at screening and baseline visits; CGI-S score ≥ 4 at screening and baseline visits. **Method of diagnosis:** SCID. **Age:** range 18-75 years. **Sex:** 73% women. **Location:** US. **Comorbidities:** none. **Adjunctive therapy:** not reported. **Adjunctive medication:** not reported. **Sample size:** vortioxetine 10 mg/d: 155; vortioxetine 20 mg/d: 150; placebo: 157. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 10 mg/day. • vortioxetine 20 mg/day. • placebo. Treatment remained undisclosed to participant and study doctor throughout study. Participants in vortioxetine group 20 mg/d received vortioxetine 10 mg/day in week 1 and 20 mg/day in weeks 2-8. Study medication given as capsules in identical blister packs. All participants took 1 capsule orally at the same time each day throughout study. Overall duration 13 weeks.
Outcomes	**Time points for assessment:** 8 weeks' treatment and 4 weeks' follow-up. **Primary outcome:** • change from baseline in MADRS total score. **Secondary outcomes:** • % participants with MADRS response at week 8; • mean CGI-I score at week 8; • change from baseline in MADRS total score at week 8 in participants with baseline HAM-A total score ≥ 20;

Jacobsen 2015 *(Continued)*

- % participants in MADRS remission at week 8;
- change from baseline in SDS total score at week 8.

Notes	**Date of study:** 2010 to 2012. **Funding source:** Takeda.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised," no details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical blister packs to maintain blinding."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal dropout rates below 20%; ITT analyses used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Jain 2013

Methods	**Study design:** multicentre, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.
Participants	**Diagnosis:** MDE as primary diagnosis according to DSM-IV-TR criteria; reported duration of current MDE ≥ 3 months; MADRS total score ≥ 30. **Method of diagnosis:** MINI. **Age:** range 18-75 years. **Sex:** 58% women. **Location:** US. **Comorbidities:** none. **Adjunctive therapy:** not reported. **Adjunctive medication:** none. **Sample size:** vortioxetine: 300; placebo: 300.

Jain 2013 *(Continued)*

	Setting: outpatients.
Interventions	Participants were randomly assigned to 1 of 2 treatments: • vortioxetine 5 mg/day; • placebo. 6-week double-blind treatment period. Centralised computer system used for participant randomisation and study medication assignments. Participants returned to study site weekly to receive wallet cards of either vortioxetine 5 mg or placebo capsules (beginning at baseline) and for efficacy and safety assessments. Blinding of all participants maintained throughout study. All study medication identical in appearance and dispensed using unique identification numbers.
Outcomes	**Time points for assessment:** 6-week treatment period and a safety follow-up 4 weeks after the last dose of double-blind study drug. **Primary outcome:** • change from baseline in HAM-D-24 total score at week 6; • change from baseline in HAM-D-24 total score at other weeks assessed. **Secondary outcomes:** • % responders in HAM-D-24 total score by study visit; • % participants in MADRS remission at week 6; • % participants with a sustained response in HAM-D-24; • change from baseline in MADRS total score; • change from baseline in HAM-A; • change from baseline in CGI-S; • CGI-I; • change from baseline in MADRS - self-assessment; • change from baseline in SF-36 at week 6; • change from baseline in SDS total score at week 6; • healthcare resource utilisation as assessed by the Health Economic Assessment Questionnaire.
Notes	**Date of study:** April-November 2008. **Funding source:** Takeda; H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A centralised computer system was used for subject randomisation and study medication assignments."
Allocation concealment (selection bias)	Low risk	Quote: "A centralized computer system was used for subject randomisation and study medication assignments." "All study medication was identical in appearance and dispensed using unique identification numbers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of all participants was maintained throughout the study. All study medication was identical in appearance and dispensed using unique identification numbers."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.

Jain 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate > 20% in placebo arm.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Katona 2012

Methods	**Study design:** randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study.
Participants	**Diagnosis:** clinical diagnosis of recurrent MDE according the DSM-IV-TR criteria; reported duration of current episode ≥ 4 weeks; MADRS total score ≥ 26; ≥ 1 previous MDE before age of 60 years. **Method of diagnosis:** MINI. **Age:** range 65-88 years. **Sex:** 66% women. **Location:** multinational (Canada, Finland, France, Germany, Sweden, Ukraine, and the US). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal behaviour therapy or systematic psychotherapy excluded. **Adjunctive medication:** antiarrhythmics, antihypertensives (except metoprolol and class 1C antiarrhythmics), proton pump inhibitors and aspirin as antiplatelet treatment allowed; occasional use of zolpidem, zopiclone and zaleplon for insomnia allowed. **Sample size:** vortioxetine: 156; duloxetine: 151; placebo: 145. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 5 mg/day; • duloxetine 60 mg/day; • placebo. 8-week double-blind treatment period. Participants were seen weekly during first 2 weeks of treatment and then every 2 weeks. Study medication given as capsules of identical appearance. Following randomisation, participants instructed to take 1 capsule per day, orally, preferably in morning.
Outcomes	**Time points for assessment:** 8 weeks' treatment and follow-up 4 weeks after completion or withdrawal. **Primary outcome:** • change from baseline in HAM-D-24 total score after 8 weeks of treatment. **Secondary outcomes:** • change from baseline in HAM-D-24 total score after 6 weeks of treatment; • change from baseline in HAM-D-24 total score after 4 weeks of treatment;

Katona 2012 *(Continued)*

- change from baseline in HAM-D-24 total score after 2 weeks of treatment;
- change from baseline in HAM-D-24 total score after 1 week of treatment;
- change from baseline in MADRS total score after 8 weeks of treatment;
- change from baseline in HAM-A total score after 8 weeks of treatment;
- change from baseline in CGI-S score after 8 weeks of treatment;
- change in clinical status using CGI-I score at week 8;
- change from baseline in GDS total score after 8 weeks of treatment;
- proportion of responders at week 8 (response defined as ≥ 50% reduction in HAM-D-24 total score);
- proportion of remitters at week 8 (remission defined as MADRS total score ≤ 10);
- risk of suicidality using C-SSRS scores.

Notes	**Date of study:** 2009-2010. **Funding source:** H. Lundbeck A/S. Those who completed the 8-week, double-blind treatment entered a 1-week, double-blind, taper-down period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were assigned to double-blind treatment according to a computer-generated randomisation list."
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were contained in a set of sealed opaque envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "All investigators, trial personnel and patients were blinded to treatment assignment for the duration of the study." "Study medication was given as capsules of identical appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts equally distributed; MMRM and LOCF methods applied.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Mahableshwarkar 2013

Methods	**Study design:** randomised, double-blind, parallel-group, placebo-controlled, active-referenced, fixed-dose study.
Participants	**Diagnosis:** MDE as primary diagnosis according to DSM-IV-TR criteria; reported duration of current MDE ≥ 3 months. **Method of diagnosis:** not reported.

Mahableshwarkar 2013 *(Continued)*

Age: range 18-75 years.

Sex: 63% women.

Location: US.

Comorbidities: none.

Adjunctive therapy: not reported.

Adjunctive medication: not reported.

Sample size: vortioxetine 2.5 mg/d: 153; vortioxetine 5 mg/d: 153; duloxetine: 152; placebo: 153.

Setting: unclear.

Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 2.5 mg/day; • vortioxetine 5 mg/day; • duloxetine 60 mg/day; • placebo. 8-week treatment period. Randomisation schedule generated by Takeda Global Research & Development, Inc., and investigators informed of each participant's coded treatment allocation by an interactive voice-activated system. All study drugs administered as identical-looking capsules and both participants and investigators blinded to treatment allocation.
Outcomes	**Time points for assessment:** 8-week double-blind treatment period and 4-week safety follow-up period. **Primary outcome:** • change from baseline in HAM-D-24 total score at week 8. **Secondary outcomes:** • change from baseline in HAM-D-24 total score at other weeks assessed; • % responders in HAM-D-24 total score by study visit; • % participants with a sustained response in HAM-D-24; • % participants in MADRS remission at week 8; • change from baseline in MADRS total score; • CGI-I scale at baseline and weeks 1, 2, 4, 6 and 8; • change from baseline in MADRS - Self-assessment; • change from baseline in HAM-A total score at baseline and weeks 1, 2, 4, 6 and 8; • change from baseline in CGI-S scale at baseline and weeks 1, 2, 4, 6 and 8; • change from baseline in SDS total score at baseline and week 8; • healthcare resource utilisation as assessed by Health Economic Assessment Questionnaire at baseline and week 8.
Notes	**Date of study:** 2008. **Funding source:** Takeda; H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details regarding the randomisation available.

Mahableshwarkar 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule was generated by Takeda Global Research & Development, Inc., and investigators were informed of each patient's coded treatment allocation by an interactive voice-activated system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "identical looking capsules and both participants and investigators were blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates > 20% in all arms.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Mahableshwarkar 2015a

Methods	**Study design:** phase 3, multicentre, randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study.
Participants	**Diagnosis:** MDE recurrent as primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x) confirmed by SCID; reported duration of current MDE ≥ 3 months; MADRS total score ≥ 26 at screening and baseline visits; CGI-S score ≥ 4 at screening and baseline visits. **Method of diagnosis:** SCID. **Age:** range 18-75 years. **Sex:** 74% women. **Location:** US. **Comorbidities:** none. **Adjunctive therapy:** people receiving formal cognitive or behavioural therapy or systematic psychotherapy excluded. **Adjunctive medication:** none. **Sample size:** vortioxetine 15 mg/d: 147; vortioxetine 20 mg/d: 154; duloxetine: 152; placebo: 161. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 15 mg/day; • vortioxetine 20 mg/day; • duloxetine 60 mg/day; • placebo. 8-week double-blind treatment period. Eligible people randomised (1:1:1:1) to receive placebo, vortioxetine 15 mg, vortioxetine 20 mg or duloxetine 60 mg once daily during 8-week, double-blind treatment

Mahableshwarkar 2015a *(Continued)*

	period, using an interactive voice response system. Following randomisation, doses were uptitrated after first week of double-blind period. Participants assigned to receive vortioxetine 15 mg/day or 20 mg/day received a 10-mg dose for first week of 8-week study, and participants assigned to receive duloxetine 60 mg/day received a 30-mg dose for first week.
Outcomes	**Time points for assessment:** 8 weeks' treatment. **Primary outcome:** • change from baseline in MADRS total score. **Secondary outcomes:** • % participants with MADRS response at week 8; • mean CGI-I score at week 8; • change from baseline in MADRS total score at week 8 in participants with baseline HAM-A total score ≥ 20; • % participants in MADRS remission at week 8; • change from baseline in SDS total score at week 8.
Notes	**Date of study:** 2010-2012. **Funding source:** Takeda.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Procedure not described in detail.
Allocation concealment (selection bias)	Low risk	Central randomisation; "interactive voice response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; placebo - matching capsules administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates > 20% in vortioxetine and control group.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Mahableshwarkar 2015b

Methods	**Study design:** randomised, double-blind, parallel-group, placebo-controlled, active-referenced, flexible-dose study.

Mahableshwarkar 2015b *(Continued)*

Participants	**Diagnosis:** recurrent MDD as primary diagnosis according to DSM-IV-TR criteria (classification code 296.3x). Current MDE confirmed using Mini International Neuropsychiatric Interview V6.0.0; MADRS total score ≥ 26 at screening and baseline; reported duration of current MDE ≥ 3 months. **Method of diagnosis:** MINI, past medical records. **Age:** range 18-65 years. **Sex:** 65% women. **Location:** multinational (Bulgaria, Finland, Germany, Poland, Russia Federation, Ukraine and US). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal cognitive or behavioural therapy or systematic psychotherapy excluded. **Adjunctive medication:** not reported. **Sample size:** vortioxetine: 198; duloxetine: 210; placebo: 194. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 10-20 mg/day: 10 mg, capsules, orally, once daily for 1 week; then dose adjustment to a maximum 20 mg, capsules, orally, once daily for up to 7 weeks; • duloxetine 60 mg/day: capsules, orally, for up to 8 weeks; duloxetine 30 mg, capsule, orally, once daily for 1 week taper-down period; • placebo: matching capsules, orally, once daily for up to 9 weeks (included 1 week taper-down period).
Outcomes	**Time points for assessment:** 8-weeks' treatment period, 1-week taper-down period. **Primary outcome:** • change from baseline to week 8 in DSST. **Secondary outcomes:** • change from baseline to week 8 in PDQ Attention/Concentration and Planning/Organization Subscore; • CGI-I score at week 8; • change from baseline to week 8 in TMT-A; • change from baseline to week 8 in TMT-B; • change in time from baseline to week 8 in Stroop Test; • change from baseline to week 8 in GMLT; • change from baseline to week 8 in DT; • change from baseline to week 8 in IT; • change from baseline to week 8 in One-Back Task; • proportion of cognitive dysfunction improvement due to improvement of depression; • change from baseline to week 8 in MADRS total score; • % participants with MADRS response at week 8; • % participants in MADRS remission at week 8; • change from baseline to week 8 in CGI-S score.
Notes	**Date of study:** 2012-2014. **Funding source:** Takeda.

Mahableshwarkar 2015b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind," "matching capsules."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal and low dropout rates; ITT analysis used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Mahableshwarkar 2015c

Methods	**Study design:** phase 3, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.
Participants	**Diagnosis:** MDE recurrent as primary diagnosis according to DSM-IV-TR criteria; reported duration of current MDE ≥ 3 months; MADRS total score ≥ 26 at screening and baseline; CGI-S score ≥ 4 at screening and baseline. **Method of diagnosis:** SCID - Clinical Trial version. **Age:** range 18-75 years. **Sex:** 70% women. **Location:** US. **Comorbidities:** none. **Adjunctive therapy:** people receiving formal cognitive or behavioural therapy or systematic psychotherapy excluded. **Adjunctive medication:** not reported. **Sample size:** vortioxetine 10 mg/d: 157; vortioxetine 15 mg/d: 152; placebo: 160. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 10 mg/day: encapsulated tablets, orally, once daily for up to 8 weeks;

Mahableshwarkar 2015c *(Continued)*

	• vortioxetine 15 mg/day: vortioxetine 10 mg, encapsulated tablets, orally, once daily for 1 week, then vortioxetine 15 mg, encapsulated tablets, orally, once daily for up to 7 weeks; • placebo: matching capsules, orally, once daily for up to 8 weeks. All participants took 1 capsule at the same time each day throughout the study. Overall time to participate up to 14 weeks. Participants made 7 visits to clinic.
Outcomes	**Time points for assessment:** 8 weeks' treatment period and 4 weeks later safety follow-up. **Primary outcome:** • change from baseline in MADRS total score. **Secondary outcomes:** • % participants with MADRS response at week 8; • mean CGI-I score at week 8; • change from baseline in MADRS total score at week 8 in participants with baseline HAM-A total score ≥ 20; • % participants in MADRS remission at week 8; • change from baseline in SDS total score.
Notes	**Date of study:** 2010-2012. **Funding source:** Takeda.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised", no details reported.
Allocation concealment (selection bias)	Low risk	Central randomisation, "interactive voice system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-matching capsules administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal and low dropout rates; ITT analysis used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

McIntyre 2014

Methods	**Study design:** randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.

McIntyre 2014 *(Continued)*

Participants	**Diagnosis:** recurrent MDD according to DSM-IV-TR criteria (classification code 296.3x). Current MDE confirmed using MINI; MADRS total score ≥ 26; reported duration of current MDE ≥ 3 months. **Method of diagnosis:** MINI. **Age:** range 18-65 years. **Sex:** 66% women. **Location:** multinational (Australia, Canada, Finland, France, Germany, Latvia, Mexico, Serbia, Slovakia, South Africa, Ukraine, and US). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal psychological treatments excluded. **Adjunctive medication:** antiarrhythmics, antihypertensives (except metoprolol, carvedilol, timolol and class 1C antiarrhythmics) and proton pump inhibitors (except omeprazole and cimetidine) allowed; episodic use of zolpidem, zopiclone or zaleplon for severe insomnia allowed for maximum 2 days per week, but not the night before a study visit. **Sample size:** vortioxetine 10 mg/d: 195; vortioxetine 20 mg/d: 207; placebo: 196. **Setting:** inpatients and outpatients.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 10 mg/day; • vortioxetine 20 mg/day; • placebo. 8-week double-blind treatment period. Participants seen at baseline and weeks 1, 4 and 8. Treatments given as capsules of identical appearance. Following randomisation, participants took 1 capsule per day, orally, preferably in morning.
Outcomes	**Time points for assessment:** 8 weeks' treatment period and 4 weeks' follow-up. **Primary outcome:** • change from baseline to week 8 in DSST (number of correct symbols) and RAVLT (Acquisition and Delayed Recall) using the composite Z-score. Defined as weighted sum of individual patient Z-scores. **Secondary outcomes:** • change from baseline to week 8 in DSST (number of correct symbols); • change from baseline to week 8 in RAVLT (Acquisition); • change from baseline to week 8 in RAVLT (Delayed Recall); • change from baseline to week 8 in TMT-A (Speed of Processing); • change from baseline to week 8 in TMT-B (Executive Function); • change from baseline to week 8 in congruent Stroop Time to Complete (Executive Function); • change from baseline to week 8 in incongruent Stroop Time to Complete (Executive Function); • change from baseline to week 8 in the SRT (Speed of Processing); • change from baseline to week 8 in the CRT (Attention); • change from baseline to week 8 in MADRS total score; • change from baseline to week 8 in CGI-S score; • clinical status using CGI-I score at week 8; • proportion of responders at week 8 (response defined as ≥ 50% decrease in the MADRS total score from baseline); • proportion of remitters at week 8 (remission defined as a MADRS total score ≤ 10); • change from baseline to week 1 using MADRS total score and composite Z-score;

McIntyre 2014 *(Continued)*

- change from baseline to week 8 using MADRS total score and composite Z-score;
- risk of suicidality using C-SSRS scores.

Notes	**Date of study:** 2011-2013. **Funding source:** H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were assigned to double-blind treatment according to a randomisation list that was computer generated by H. Lundbeck A/S."
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were contained in a set of sealed opaque envelopes [...]. The randomisation code was not broken for any patient during the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study medications were given as capsules of identical appearance;" double-blind trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal dropout rates < 20%, ITT analyses used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

NCT01255787

Methods	**Study design:** randomised, double-blind, placebo-controlled, dose-ranging study (fixed dose).
Participants	**Diagnosis:** MDD as primary diagnosis according to DSM-IV-TR criteria (classification code 296.2x and 296.3x); reported duration of current MDE ≥ 3 months at screening visit; MADRS total score ≥ 26 at screening and baseline; CGI-S score ≥ 4 at screening and baseline. **Method of diagnosis:** MINI. **Age:** range 20-64 years. **Sex:** 63% women. **Location:** multinational (Croatia, Finland, Germany, Hong Kong, India, Japan, Korea, Republic of, Latvia, Malaysia, Philippines, Poland, Romania, Russian Federation, Serbia, Taiwan, Ukraine). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal cognitive or behavioural therapy or systematic psychotherapy excluded.

NCT01255787 *(Continued)*

	Adjunctive medication: not reported. **Sample size:** vortioxetine 5 mg/d: 144; vortioxetine 10 mg/d: 150; vortioxetine 20 mg/d: 154; placebo: 152. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 4 treatments: • vortioxetine 5 mg/day: tablets, orally, once daily for 8 weeks, followed by placebo-matching tablets, orally, once daily for 2 weeks; • vortioxetine 10 mg/day: tablets, orally, once daily for 8 weeks, followed by placebo-matching tablets, orally, once daily for 2 weeks; • vortioxetine 20 mg/day: tablets, orally, once daily for 1 week, followed by vortioxetine 20 mg, tablets, orally, once daily for 7 weeks, followed by placebo-matching tablets, orally, once daily, for 2 weeks; • placebo: matching tablets, orally, once daily for up to 10 weeks. All participants took 1 capsule at the same time each day throughout study. Participants made weekly visits to clinic during the first 2 weeks of 8-week treatment period and then every 2 weeks up to the end of the 8-week treatment period.
Outcomes	**Time points for assessment:** 8 weeks' treatment period and 4 weeks' follow-up. **Primary outcome:** • change from baseline in MADRS total score. **Secondary outcomes:** • % participants with MADRS response at week 8; • % participants in MADRS remission at week 8; • mean CGI-I score at week 8; • change from baseline in SDS total score at week 8.
Notes	**Date of study:** 2010-2012. **Funding source:** Takeda.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised," no details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo (dummy inactive pill) - this was a capsule that looked like the study drug but had no active ingredient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal and low dropout rates; ITT analysis used.

NCT01255787 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Takeda 2011

Methods	**Study design:** randomised, double-blind, placebo-controlled, parallel-group, phase 3 study.
Participants	**Diagnosis:** MDD as primary diagnosis according to DSM-IV-TR criteria (classification code 296.2x and 296.3x); reported duration of current MDE ≥ 3 months at screening visit; MADRS total score ≥ 26 at screening and baseline visits; CGI-S score ≥ 4 at screening and baseline visits. **Method of diagnosis:** not reported. **Age:** range 20-75 years. **Sex:** 47% women. **Location:** Japan. **Comorbidities:** none. **Adjunctive therapy:** not reported. **Adjunctive medication:** not reported. **Sample size:** vortioxetine 5 mg/d: 119; vortioxetine 10 mg/d: 123; placebo: 124. **Setting:** unclear.
Interventions	Participants were randomly assigned to 1 of 3 treatments: • vortioxetine 5 mg/day: tablets, orally, once daily for up to 8 weeks; • vortioxetine 10 mg/day: tablets, orally, once daily for up to 8 weeks; • placebo: matching tablets, orally, once daily for up to 8 weeks. 1-week screening period, 8-week double-blind treatment period, 4-week safety follow-up. Duration of study 13 weeks in total.
Outcomes	**Time points for assessment:** 8 weeks' treatment period and 4 weeks' follow-up. **Primary outcome:** • change from baseline in MADRS total score after 8 weeks of treatment. **Secondary outcomes:** • % participants with MADRS response after 8 weeks of treatment; • % participants with MADRS remission after 8 weeks of treatment; • change from baseline in HAM-D-17 total score after 8 weeks of treatment; • CGI-I score after 8 weeks of treatment; • change from baseline in SDS total score after 8 weeks of treatment;
Notes	**Date of study:** 2011-2012. **Funding source:** Takeda.

Risk of bias

Takeda 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomised," no details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-matching capsules were administered.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal and low dropout rates; ITT analysis used.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

Wang 2015

Methods	**Study design:** randomised, double-blind, parallel-group, active-comparator, fixed-dose study.
Participants	**Diagnosis:** recurrent MDD as primary diagnosis according to DSM-IV-TR criteria. Current MDE confirmed using MINI; MADRS total score ≥ 26; CGI-S score ≥ 4; reported duration of current MDE ≥ 3 months. **Method of diagnosis:** MINI. **Age:** range 19-65 years. **Sex:** 60% women. **Location:** multinational (China, South Korea, Taiwan and Thailand). **Comorbidities:** none. **Adjunctive therapy:** people receiving formal cognitive or behavioural therapy or systematic psychotherapy excluded. **Adjunctive medication:** occasional use of zolpidem, zopiclone and zaleplon for severe insomnia allowed (maximum 2 days/week, not the night before a study visit). **Sample size:** vortioxetine: 213; venlafaxine: 230. **Setting:** inpatients and outpatients.
Interventions	Participants were randomly assigned to 1 of 2 treatments: • vortioxetine 10 mg/day; • venlafaxine XR 50 mg/day.

Wang 2015 *(Continued)*

	8-week double-blind treatment. Participants seen at baseline and weeks 1, 2, 4, 6 and 8. Participants who completed 8-week treatment period entered a 1-week double-blind down-taper period, during which participants in vortioxetine group received placebo and participants in venlafaxine XR group received 75 mg/day.
Outcomes	**Time points for assessment:** 8 weeks' double-blind treatment and follow-up 4 weeks later. **Primary outcome:** • change from baseline in MADRS total score at week 8. **Secondary outcomes:** • change in CGI-S score from baseline to week 8; • CGI-I score at week 8; • change in HAM-A total score from baseline to week 8; • MADRS response at week 8 (response defined as ≥ 50% decrease in MADRS total score from baseline; • remission at week 8 (remission defined as MADRS total score ≤ 10); • number of adverse events from baseline to week 12.
Notes	**Date of study:** 2012-2013. **Funding source:** H. Lundbeck A/S.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The IVRS randomly allocated the patient a randomisation number according to a randomisation list that was generated by H. Lundbeck A/S, the manufacturer of vortioxetine."
Allocation concealment (selection bias)	Low risk	Quote: "using an interactive voice/web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...medication was given as venlafaxine XR capsules or encapsulated vortioxetine tablets of identical appearance;" "The randomisation code was not broken for any patient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate > 20% in control (venlafaxine) group.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	Drug company sponsored trial.

ASEX: Arizona Sexual Experience Scale; C-SSRS: Columbia Suicide Severity Rating Scale; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity; CRT: Cognitive Reflection Test; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSST: Digit Symbol Substitution Test; DT: Detection Task; GDS: Geriatrics Depression Scale; GMLT: Groton Maze Learning Test; HAD: Hospital Anxiety and Depression; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-D-24: 24-item Hamilton Depression Scale; IT: Identification Task; ITT: intention to treat; LOCF: last observation carried forward; MADRS: Montgomery-Åsberg Depression Scale; MDD: major depressive disorder; MDE: major depressive episode; MINI: Mini

International Neuropsychiatric Interview; MMRM: mixed model for repeated measurement; PDQ: Perceived Deficits Questionnaire; RAVLT: Rey Auditory Verbal Learning Task; SCID: Structured Clinical Interview for DSM Disorders; SDS: Sheehan Disability Scale; SF-36: 36-Item Short-Form Health Survey; SRT: Simple Reaction Time; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Boulenger 2012	Relapse prevention study.
Browning 2014	Functional magnetic resonance imaging study that randomised remitted participants and healthy controls.
Jacobsen 2015a	Compared switching to vortioxetine vs escitalopram in participants who responded to citalopram, paroxetine or sertraline. Treatment and dosage had to be stable for 8 weeks before randomisation.
Jacobsen 2015b	Open-label extension study including people completing Mahableshwarkar 2015a; Jacobsen 2015; or Mahableshwarkar 2015c.
Montgomery 2014	Compared switching to vortioxetine vs agomelatine in people with inadequate response to ≥ 6 weeks' treatment with selective serotonin re-uptake inhibitors (citalopram, escitalopram, paroxetine) or serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine).
NCT02371980	Relapse prevention study (ongoing).

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT02272517

Methods	8-week, randomised, double-blind, active controlled trial.
Participants	Recurrent MDD as the primary diagnosis according to DSM-IV-TR criteria confirmed using MINI; PHQ-9 score ≥ 14; MADRS total score ≥ 22; CGI-S score ≥ 4; duration of current episode ≤ 1 year. Age: 18-65 years. Location: Finland, Germany, Serbia and Slovakia.
Interventions	Vortioxetine: 10-20 mg/day. Escitalopram: 10-20 mg/day.
Outcomes	Primary outcome: change in DSST. Secondary outcomes: various cognitive test, change in PDQ-D, change in PHQ-9 (depressive symptoms), CGI-S, CGI-I, C-SSRS.
Notes	

NCT02279966

Methods	8-week, randomised, double-blind, placebo- and active-controlled trial.
Participants	MDD as primary diagnosis according to DSM-IV-TR criteria confirmed using MINI; MADRS total score ≥ 26; duration of current episode ≥ 3 months.

NCT02279966 *(Continued)*	
	Age: 18-65 years. Location: Estonia, Finland, Germany and Lithuania.
Interventions	Vortioxetine 10 mg/day. Paroxetine 20 mg/day. Placebo.
Outcomes	Primary outcome: change in DSST (number of correct symbols). Secondary outcomes: various cognitive tests, change in PDQ-D, change in PHQ-9 (depressive symptoms), CGI-S, CGI-I, C-SSRS, MADRS.
Notes	

C-SSRS: Columbia Suicide Severity Rating Scale; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSST: Digit Symbol Substitution Test; MADRS: Montgomery-Åsberg Depression Scale; MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; PDQ-D: Perceived Deficits Questionnaire - Depression; PHQ-9: Patient Health Questionnaire-9.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02294305	
Trial name or title	Vortioxetine versus Placebo in Major Depressive Disorder Comorbid with Social Anxiety Disorder.
Methods	12-week, randomised, double-blind, placebo-controlled trial.
Participants	MDD and SAD according to DSM-V criteria confirmed using MINI; MADRS total score ≥ 26; CGI-S (composite for MDD and SAD) ≥ 4; duration of current depressive episode ≥ 4 weeks; duration of SAD ≥ 6 months. Age: 18-70 years. Location: US.
Interventions	Vortioxetine 10-20 mg/day. Placebo.
Outcomes	Primary outcome: CGI-I responder rate. Secondary outcomes: change in MADRS total score, change in Liebowitz Social Anxiety Scale total score.
Starting date	
Contact information	
Notes	

NCT02389816	
Trial name or title	A Phase 3 Study of Lu AA21004 in Patients with Major Depressive Disorder.

NCT02389816 *(Continued)*

Methods	8-week, randomised, double-blind, placebo-controlled trial.
Participants	Recurrent MDD as primary diagnosis according to DSM-IV-TR; MADRS total score ≥ 26; HAM-D-17 total score ≥ 18; CGI-S ≥ 4; duration of current depressive episode 3-12 months. Age: 20-75 years. Location: Japan.
Interventions	Vortioxetine 10 mg/day. Vortioxetine 20 mg/day. Placebo.
Outcomes	Primary outcome: change from baseline in MADRS. Secondary outcomes: MADRS response and remission, change in HAM-D, CGI, SDS, DSST and PDQ-5.
Starting date	April 2015.
Contact information	Takeda Study Registration Call Center, tel: +1-800-778-2860 (USA and EU); email: medicalinformation@tpna.com.
Notes	

CGI: Clinical Global Impression; CGI-I: Clinical Global Impression - Improvement; CGI-S: Clinical Global Impression - Severity; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSST: Digit Symbol Substitution Test; HAM-D: Hamilton Depression Scale; HAM-D-17: 17-item Hamilton Depression Scale; MADRS: Montgomery-Åsberg Depression Scale; MDD: major depressive disorder; MINI: Mini International Neuropsychiatric Interview; PDQ-5: Perceived Deficits Questionnaire; SAD: social anxiety disorder; SDS: Sheehan Disability Scale.

DATA AND ANALYSES

Comparison 1. Vortioxetine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.22, 1.49]
2 Total number of dropouts	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
3 Remission	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.15, 1.53]
4 Depressive symptoms	14	5566	Mean Difference (IV, Random, 95% CI)	-2.94 [-4.07, -1.80]
5 Dropout due to adverse events	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.09, 1.81]
6 Dropout due to inefficacy	14	6220	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.34, 0.90]
7 Tolerability	14	6182	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.07, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Subgroup analysis: fixed vs flexible dosing - response	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.22, 1.49]
8.1 Fixed dose	12	5513	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.19, 1.52]
8.2 Flexible dose	2	707	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.16, 1.63]
9 Subgroup analysis: fixed vs flexible dosing - total number of dropouts	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
9.1 Fixed dose	12	5513	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.22]
9.2 Flexible dose	2	707	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.64, 1.30]
10 Subgroup analysis: inclusion of older (aged > 65 years) participants - response	10	4525	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.24, 1.54]
10.1 Older participants included	6	2616	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.15, 1.55]
10.2 Older participants excluded	4	1909	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.23, 1.71]
11 Subgroup analysis: inclusion of older (aged > 65 years) participants - total number of dropouts	10	4528	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.96, 1.28]
11.1 Older participants included	6	2619	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.05, 1.49]
11.2 Older participants excluded	4	1909	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.13]
12 Sensitivity analysis - exclusion > 20% dropouts - response	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.22, 1.49]
12.1 < 20% dropouts	9	3927	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.26, 1.57]
12.2 > 20% dropouts	5	2293	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.03, 1.52]
13 Sensitivity analysis - exclusion > 20% dropouts - total number of dropouts	14	6220	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
13.1 < 20% dropout	9	3927	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.21]
13.2 > 20% dropout	5	2293	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.91, 1.28]
14 Adverse events	14		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Constipation	11		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Nausea	14		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Diarrhoea	13		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.4 Dry mouth	12		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.5 Vomiting	9		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.6 Abdominal pain upper	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.7 Dyspepsia	7		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.8 Gastro-oesophageal reflux disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.9 Abdominal discomfort	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.10 Abdominal pain	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.11 Stomach discomfort	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.12 Flatulence	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.13 Fatigue	12		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.14 Pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.15 Thirst	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.16 Irritability	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.17 Decreased appetite	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.18 Increased appetite	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.19 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.20 Headache	14		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.21 Dizziness	13		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.22 Somnolence	10		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.23 Tremor	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.24 Sedation	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.25 Dysgeusia	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.26 Hypoaesthesia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.27 Poor-quality sleep	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.28 Ejaculation delayed (men)	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.29 Erectile dysfunction (men)	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.30 Dysmenorrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.31 Hyperhidrosis	9		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.32 Pruritus generalised	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.33 Pruritus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.34 Vision blurred	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.35 Nasopharyngitis	11		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.36 Influenza	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.37 Respiratory tract infection	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.38 Gastroenteritis viral	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.39 Sinusitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.40 Urinary tract infection	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.41 Bronchitis	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.42 Anorgasmia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.43 Insomnia	9		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.44 Restlessness	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.45 Abnormal dreams	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.46 Anxiety	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.47 Depression	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.48 Libido decreased	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.49 Orgasm abnormal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.50 Nightmare	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.51 Middle insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.52 Suicidal ideation	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.53 Tachycardia	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.54 Palpitations	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.55 Tinnitus	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.56 Back pain	7		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.57 Arthralgia	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.58 Myalgia	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.59 Musculoskeletal pain	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.60 Muscle spasms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.61 Pain in extremity	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.62 Hypertension	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.63 Hot flush	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.64 Fall	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.65 Ligament sprain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.66 Muscle strain	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.67 Accidental overdose	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.68 Road traffic accident	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.69 Nasal congestion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.70 Yawning	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.71 Rhinorrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.72 Oropharyngeal pain	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.73 Weight decreased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.74 Blood pressure increased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.75 Hepatic function abnormal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Serious adverse events	14		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1 Varicella zoster infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Kidney infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.3 Herpes zoster infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

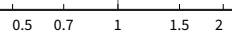
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.4 Puncture site infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.5 Gastroenteritis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.6 Pyelonephritis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.7 Brain tumour	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.8 Gallbladder cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.9 Colon cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.10 Laryngeal cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.11 Renal cell carcinoma	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.12 Bile duct cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.13 Prostate cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.14 Breast cancer recurrent	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.15 Worsening of major depressive disorder	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.16 Suicidal ideation	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.17 Suicide attempt	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.18 Intentional self-injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.19 Self-injurious behaviour	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.20 Panic attack	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.21 Suicidal behaviour	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.22 Middle ear effusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.23 Jaundice cholestatic	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.24 Cholecystitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.25 Pelvic fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.26 Intentional overdose	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.27 Lumbar vertebral fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.28 Injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.29 Hip fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.30 Head injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.31 Stress fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.32 Craniocerebral injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.33 Subdural haematoma	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.34 Brain contusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.35 Road traffic accident	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.36 Serotonin syndrome	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.37 Dizziness	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.38 Cerebrovascular accident	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.39 Convulsion	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.40 Transient ischaemic attack	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.41 Lumbar radiculopathy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.42 Syncope	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.43 Cerebral haematoma	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.44 Subarachnoid haemorrhage	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.45 Adenomyosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.46 Vaginal haemorrhage	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.47 Pulmonary embolism	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.48 Blood pressure decreased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.49 Tachycardia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.50 Acute myocardial infarction	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.51 Atrial fibrillation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.52 Coronary artery disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.53 Pancreatitis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.54 Hiatus hernia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.55 Drug hypersensitivity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.56 Abortion spontaneous	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.57 Ectopic pregnancy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.58 Abortion missed	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.59 Abortion induced	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.60 Type 1 diabetes mellitus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.61 Hypertension	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.62 Renal colic	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Vortioxetine versus placebo, Outcome 1 Response.

Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	140/210	47/105		7.55%	1.49[1.18,1.88]
Baldwin 2012	174/312	68/152		8.33%	1.25[1.02,1.53]
Boulenger 2014	178/303	51/158		7.26%	1.82[1.42,2.32]
Henigsberg 2012	129/280	34/140		5.65%	1.9[1.38,2.61]
Jacobsen 2015	110/305	44/157		6.19%	1.29[0.96,1.72]
Jain 2013	135/300	132/300		8.96%	1.02[0.86,1.22]
Katona 2012	82/156	51/145		6.75%	1.49[1.14,1.95]
Mahableshwarkar 2013	58/153	48/153		5.83%	1.21[0.89,1.65]
Mahableshwarkar 2015a	129/301	60/161		7.39%	1.15[0.91,1.46]
Mahableshwarkar 2015b	89/198	69/194		7.27%	1.26[0.99,1.61]
Mahableshwarkar 2015c	107/309	49/160		6.47%	1.13[0.86,1.49]
McIntyre 2014	212/404	57/198		7.42%	1.82[1.44,2.31]
NCT01255787	226/448	59/152		7.88%	1.3[1.04,1.62]
Takeda 2011	117/242	49/124		7.04%	1.22[0.95,1.58]
Total (95% CI)	**3921**	**2299**		**100%**	**1.35[1.22,1.49]**
Total events: 1886 (Vortioxetine), 818 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=32.11, df=13(P=0); I^2=59.51%					
Test for overall effect: Z=5.66(P<0.0001)					



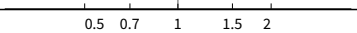
Analysis 1.2. Comparison 1 Vortioxetine versus placebo, Outcome 2 Total number of dropouts.

Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	30/210	18/105		4.98%	0.83[0.49,1.42]
Baldwin 2012	73/312	29/152		9.67%	1.23[0.84,1.8]
Boulenger 2014	61/303	25/158		7.94%	1.27[0.83,1.94]
Henigsberg 2012	29/280	13/140		3.69%	1.12[0.6,2.08]
Jacobsen 2015	59/305	18/157		5.9%	1.69[1.03,2.76]
Jain 2013	56/300	64/300		13.84%	0.88[0.63,1.21]
Katona 2012	20/156	17/145		3.89%	1.09[0.6,2]
Mahableshwarkar 2013	31/153	33/153		7.5%	0.94[0.61,1.45]
Mahableshwarkar 2015a	75/301	32/161		10.59%	1.25[0.87,1.81]
Mahableshwarkar 2015b	30/198	30/194		6.57%	0.98[0.62,1.56]
Mahableshwarkar 2015c	57/309	27/160		8.23%	1.09[0.72,1.66]
McIntyre 2014	53/404	35/198		9.3%	0.74[0.5,1.1]
NCT01255787	57/448	16/152		5.21%	1.21[0.72,2.04]
Takeda 2011	17/242	11/124		2.7%	0.79[0.38,1.64]
Total (95% CI)	**3921**	**2299**		**100%**	**1.05[0.93,1.19]**
Total events: 648 (Vortioxetine), 368 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=12.16, df=13(P=0.51); I^2=0%					
Test for overall effect: Z=0.83(P=0.4)					

Favours vortioxetine — Favours placebo

Analysis 1.3. Comparison 1 Vortioxetine versus placebo, Outcome 3 Remission.

Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	102/210	29/105		7.42%	1.76[1.25,2.47]
Baldwin 2012	110/312	49/152		8.64%	1.09[0.83,1.44]
Boulenger 2014	110/303	30/158		7.15%	1.91[1.34,2.73]
Henigsberg 2012	77/280	23/140		6.11%	1.67[1.1,2.55]
Jacobsen 2015	66/305	22/157		5.77%	1.54[0.99,2.4]
Jain 2013	85/300	92/300		9.18%	0.92[0.72,1.18]
Katona 2012	45/156	28/145		6.19%	1.49[0.99,2.26]
Mahableshwarkar 2013	32/153	33/153		5.93%	0.97[0.63,1.49]
Mahableshwarkar 2015a	82/301	41/161		7.74%	1.07[0.77,1.48]
Mahableshwarkar 2015b	53/198	36/194		6.82%	1.44[0.99,2.1]
Mahableshwarkar 2015c	72/309	33/160		6.98%	1.13[0.78,1.63]
McIntyre 2014	135/404	33/198		7.41%	2[1.43,2.82]
NCT01255787	124/448	40/152		8.06%	1.05[0.78,1.43]
Takeda 2011	70/242	27/124		6.6%	1.33[0.9,1.96]
Total (95% CI)	**3921**	**2299**		**100%**	**1.32[1.15,1.53]**
Total events: 1163 (Vortioxetine), 516 (Placebo)					
Heterogeneity: Tau^2=0.04; Chi^2=31.11, df=13(P=0); I^2=58.21%					
Test for overall effect: Z=3.81(P=0)					



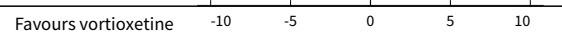
Favours placebo — Favours vortioxetine

Analysis 1.4. Comparison 1 Vortioxetine versus placebo, Outcome 4 Depressive symptoms.

Study or subgroup	Vortioxetine N	Vortioxetine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Alvarez 2012	182	-22 (9.5)	88	-15.7 (9.4)		6.52%	-6.33[-8.72,-3.94]
Baldwin 2012	241	-18.4 (8.8)	123	-15.9 (8.9)		7.28%	-2.5[-4.42,-0.58]
Boulenger 2014	300	-18 (9.6)	158	-11.7 (9.6)		7.39%	-6.32[-8.17,-4.47]
Henigsberg 2012	251	-15.4 (8.1)	128	-10.9 (8)		7.6%	-4.5[-6.21,-2.79]
Jacobsen 2015	246	-13.7 (9.3)	139	-10.8 (9.6)		7.19%	-2.9[-4.87,-0.93]
Jain 2013	292	-15.8 (11.9)	286	-15.5 (12)		7.23%	-0.32[-2.27,1.63]
Katona 2012	155	-15.5 (9.3)	145	-11.2 (9.3)		6.98%	-4.3[-6.41,-2.19]
Mahableshwarkar 2013	153	-11.3 (9.9)	149	-11.2 (10)		6.76%	-0.1[-2.34,2.14]
Mahableshwarkar 2015a	225	-14.9 (9.4)	129	-12.8 (9.5)		7.08%	-2.1[-4.14,-0.06]
Mahableshwarkar 2015b	175	-14.3 (9)	167	-12.3 (9.6)		7.18%	-2[-3.98,-0.02]
Mahableshwarkar 2015c	236	-13.5 (11.7)	126	-12.9 (11.7)		6.31%	-0.63[-3.16,1.9]
McIntyre 2014	355	-16.6 (8.4)	165	-10.9 (8.2)		7.88%	-5.7[-7.23,-4.17]
NCT01255787	438	-15.4 (9.6)	150	-14 (9)		7.61%	-1.41[-3.11,0.29]
Takeda 2011	241	-15.3 (9.7)	123	-13.8 (9.7)		6.99%	-1.5[-3.6,0.6]
Total * **	**3490**		**2076**			**100%**	**-2.94[-4.07,-1.8]**

Heterogeneity: Tau^2=3.64; Chi^2=60.58, df=13(P<0.0001); I^2=78.54%

Test for overall effect: Z=5.07(P<0.0001)



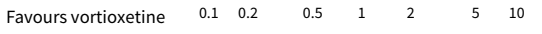
Analysis 1.5. Comparison 1 Vortioxetine versus placebo, Outcome 5 Dropout due to adverse events.

Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	10/210	4/105		4.88%	1.25[0.4,3.89]
Baldwin 2012	33/312	12/152		15.77%	1.34[0.71,2.52]
Boulenger 2014	27/303	7/158		9.62%	2.01[0.9,4.52]
Henigsberg 2012	6/280	2/140		2.5%	1.5[0.31,7.34]
Jacobsen 2015	16/305	2/157		2.96%	4.12[0.96,17.68]
Jain 2013	9/300	11/300		8.38%	0.82[0.34,1.95]
Katona 2012	10/156	6/145		6.46%	1.55[0.58,4.15]
Mahableshwarkar 2013	12/153	7/153		7.68%	1.71[0.69,4.24]
Mahableshwarkar 2015a	28/301	4/161		5.93%	3.74[1.34,10.49]
Mahableshwarkar 2015b	6/198	6/194		5.07%	0.98[0.32,2.99]
Mahableshwarkar 2015c	20/309	6/160		7.9%	1.73[0.71,4.21]
McIntyre 2014	18/404	8/198		9.46%	1.1[0.49,2.49]
NCT01255787	20/448	6/152		7.88%	1.13[0.46,2.76]
Takeda 2011	7/242	6/124		5.51%	0.6[0.21,1.74]
Total (95% CI)	**3921**	**2299**		**100%**	**1.41[1.09,1.81]**

Total events: 222 (Vortioxetine), 87 (Placebo)

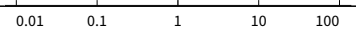
Heterogeneity: Tau^2=0; Chi^2=11.9, df=13(P=0.54); I^2=0%

Test for overall effect: Z=2.66(P=0.01)



Analysis 1.6. Comparison 1 Vortioxetine versus placebo, Outcome 6 Dropout due to inefficacy.

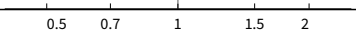
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	9/210	6/105		10.42%	0.75[0.27,2.05]
Baldwin 2012	7/312	5/152		9.32%	0.68[0.22,2.11]
Boulenger 2014	10/303	6/158		10.54%	0.87[0.32,2.35]
Henigsberg 2012	5/280	8/140		9.6%	0.31[0.1,0.94]
Jacobsen 2015	4/305	1/157		3.93%	2.06[0.23,18.27]
Jain 2013	11/300	6/300		10.65%	1.83[0.69,4.89]
Katona 2012	2/156	7/145		6.43%	0.27[0.06,1.26]
Mahableshwarkar 2013	2/153	1/153		3.39%	2[0.18,21.83]
Mahableshwarkar 2015a	2/301	9/161		6.63%	0.12[0.03,0.54]
Mahableshwarkar 2015b	1/198	6/194		4.15%	0.16[0.02,1.34]
Mahableshwarkar 2015c	2/309	4/160		5.76%	0.26[0.05,1.4]
McIntyre 2014	4/404	10/198		9.19%	0.2[0.06,0.62]
NCT01255787	6/448	2/152		6.25%	1.02[0.21,4.99]
Takeda 2011	3/242	1/124		3.73%	1.54[0.16,14.63]
Total (95% CI)	**3921**	**2299**		**100%**	**0.56[0.34,0.9]**
Total events: 68 (Vortioxetine), 72 (Placebo)					
Heterogeneity: Tau^2=0.33; Chi^2=21.88, df=13(P=0.06); I^2=40.58%					
Test for overall effect: Z=2.37(P=0.02)					



Favours vortioxetine — Favours placebo

Analysis 1.7. Comparison 1 Vortioxetine versus placebo, Outcome 7 Tolerability.

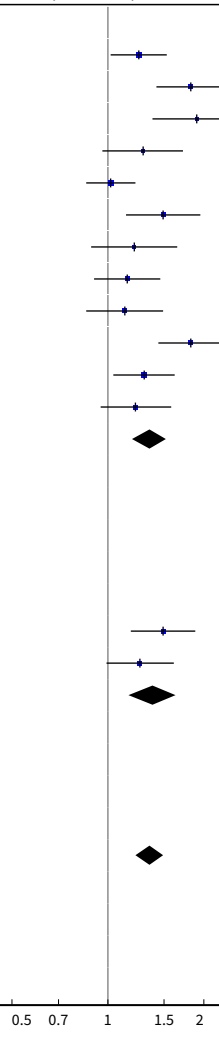
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alvarez 2012	147/208	64/105		5.53%	1.16[0.97,1.38]
Baldwin 2012	199/308	92/148		7.43%	1.04[0.89,1.21]
Boulenger 2014	186/302	80/158		5.44%	1.22[1.02,1.45]
Henigsberg 2012	137/279	60/140		3.47%	1.15[0.91,1.44]
Jacobsen 2015	217/305	98/157		8.37%	1.14[0.99,1.31]
Jain 2013	209/299	192/298		12.46%	1.08[0.97,1.21]
Katona 2012	97/156	89/145		5.44%	1.01[0.85,1.21]
Mahableshwarkar 2013	108/153	96/151		6.77%	1.11[0.95,1.3]
Mahableshwarkar 2015a	233/301	112/159		11.51%	1.1[0.98,1.24]
Mahableshwarkar 2015b	73/196	41/191		1.69%	1.74[1.25,2.41]
Mahableshwarkar 2015c	237/305	114/160		11.93%	1.09[0.97,1.22]
McIntyre 2014	199/402	75/196		4.22%	1.29[1.06,1.59]
NCT01255787	295/442	97/152		8.85%	1.05[0.91,1.2]
Takeda 2011	173/242	78/124		6.88%	1.14[0.97,1.33]
Total (95% CI)	**3898**	**2284**		**100%**	**1.12[1.07,1.16]**
Total events: 2510 (Vortioxetine), 1288 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=14.14, df=13(P=0.36); I^2=8.08%					
Test for overall effect: Z=5.01(P<0.0001)					



Favours vortioxetine — Favours placebo

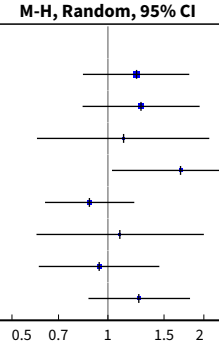
Analysis 1.8. Comparison 1 Vortioxetine versus placebo, Outcome 8 Subgroup analysis: fixed vs flexible dosing - response.

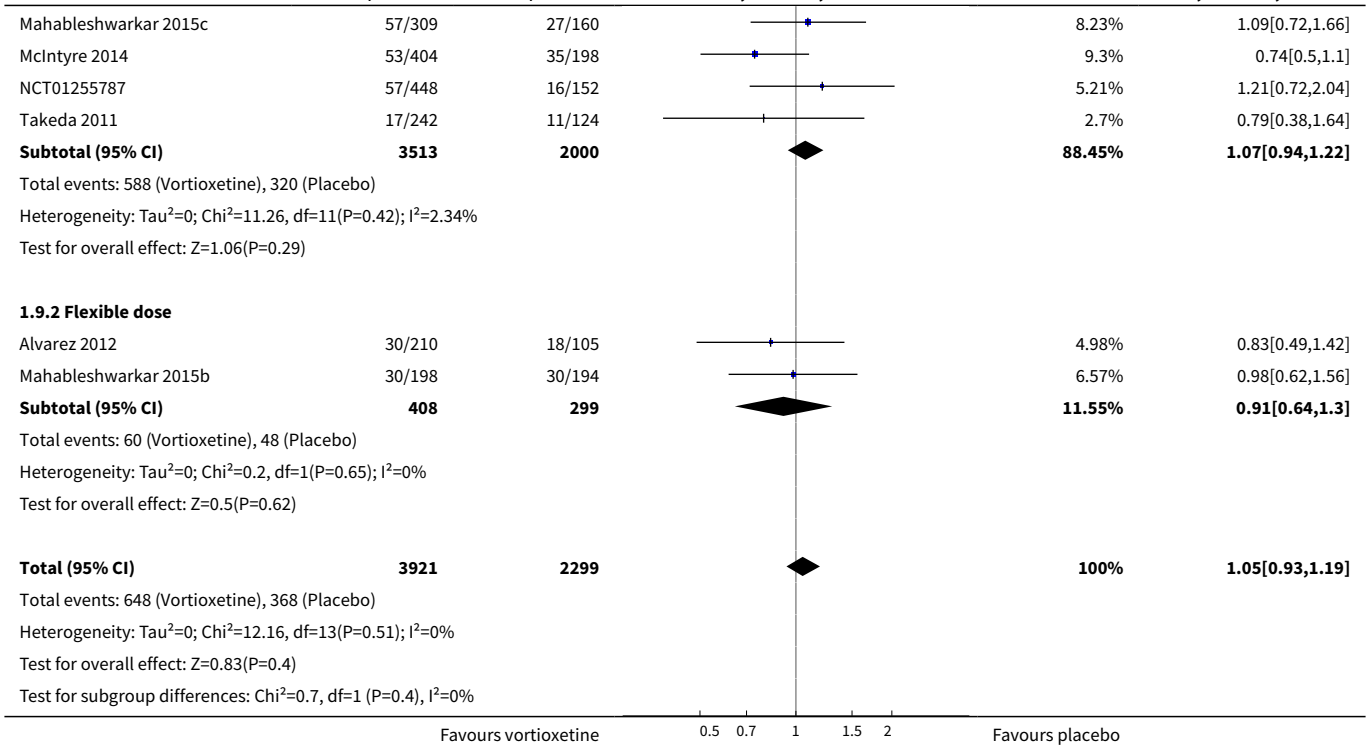
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Fixed dose					
Baldwin 2012	174/312	68/152		8.33%	1.25[1.02,1.53]
Boulenger 2014	178/303	51/158		7.26%	1.82[1.42,2.32]
Henigsberg 2012	129/280	34/140		5.65%	1.9[1.38,2.61]
Jacobsen 2015	110/305	44/157		6.19%	1.29[0.96,1.72]
Jain 2013	135/300	132/300		8.96%	1.02[0.86,1.22]
Katona 2012	82/156	51/145		6.75%	1.49[1.14,1.95]
Mahableshwarkar 2013	58/153	48/153		5.83%	1.21[0.89,1.65]
Mahableshwarkar 2015a	129/301	60/161		7.39%	1.15[0.91,1.46]
Mahableshwarkar 2015c	107/309	49/160		6.47%	1.13[0.86,1.49]
McIntyre 2014	212/404	57/198		7.42%	1.82[1.44,2.31]
NCT01255787	226/448	59/152		7.88%	1.3[1.04,1.62]
Takeda 2011	117/242	49/124		7.04%	1.22[0.95,1.58]
Subtotal (95% CI)	**3513**	**2000**		**85.18%**	**1.35[1.19,1.52]**
Total events: 1657 (Vortioxetine), 702 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=31.05, df=11(P=0); I^2=64.58%					
Test for overall effect: Z=4.84(P<0.0001)					
1.8.2 Flexible dose					
Alvarez 2012	140/210	47/105		7.55%	1.49[1.18,1.88]
Mahableshwarkar 2015b	89/198	69/194		7.27%	1.26[0.99,1.61]
Subtotal (95% CI)	**408**	**299**		**14.82%**	**1.38[1.16,1.63]**
Total events: 229 (Vortioxetine), 116 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=3.72(P=0)					
Total (95% CI)	**3921**	**2299**		**100%**	**1.35[1.22,1.49]**
Total events: 1886 (Vortioxetine), 818 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=32.11, df=13(P=0); I^2=59.51%					
Test for overall effect: Z=5.66(P<0.0001)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					



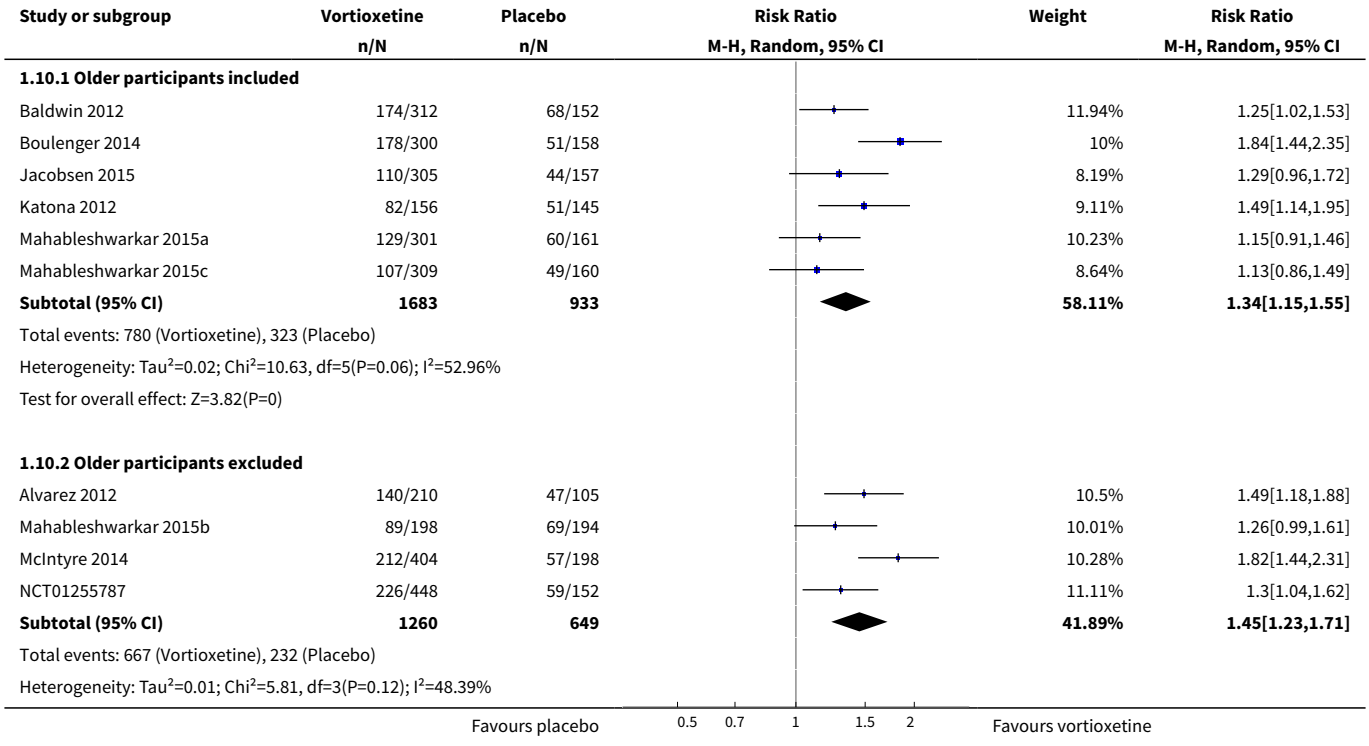
Analysis 1.9. Comparison 1 Vortioxetine versus placebo, Outcome 9 Subgroup analysis: fixed vs flexible dosing - total number of dropouts.

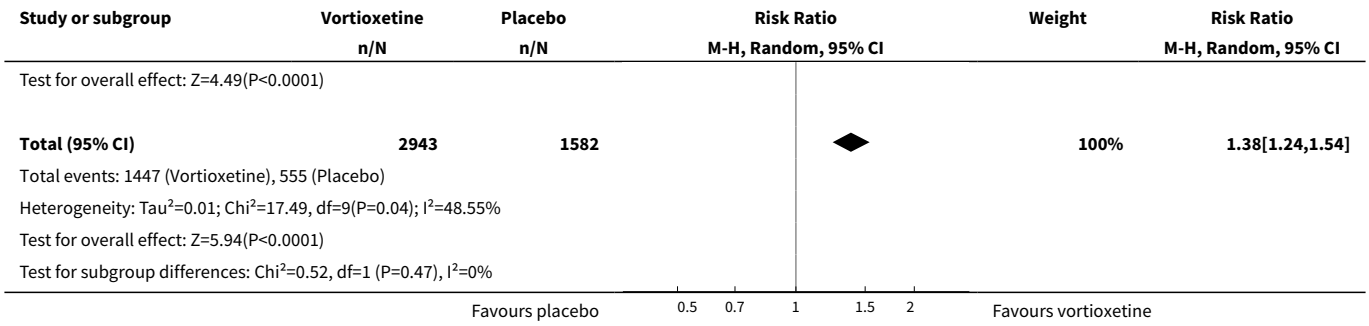
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Fixed dose					
Baldwin 2012	73/312	29/152		9.67%	1.23[0.84,1.8]
Boulenger 2014	61/303	25/158		7.94%	1.27[0.83,1.94]
Henigsberg 2012	29/280	13/140		3.69%	1.12[0.6,2.08]
Jacobsen 2015	59/305	18/157		5.9%	1.69[1.03,2.76]
Jain 2013	56/300	64/300		13.84%	0.88[0.63,1.21]
Katona 2012	20/156	17/145		3.89%	1.09[0.6,2]
Mahableshwarkar 2013	31/153	33/153		7.5%	0.94[0.61,1.45]
Mahableshwarkar 2015a	75/301	32/161		10.59%	1.25[0.87,1.81]



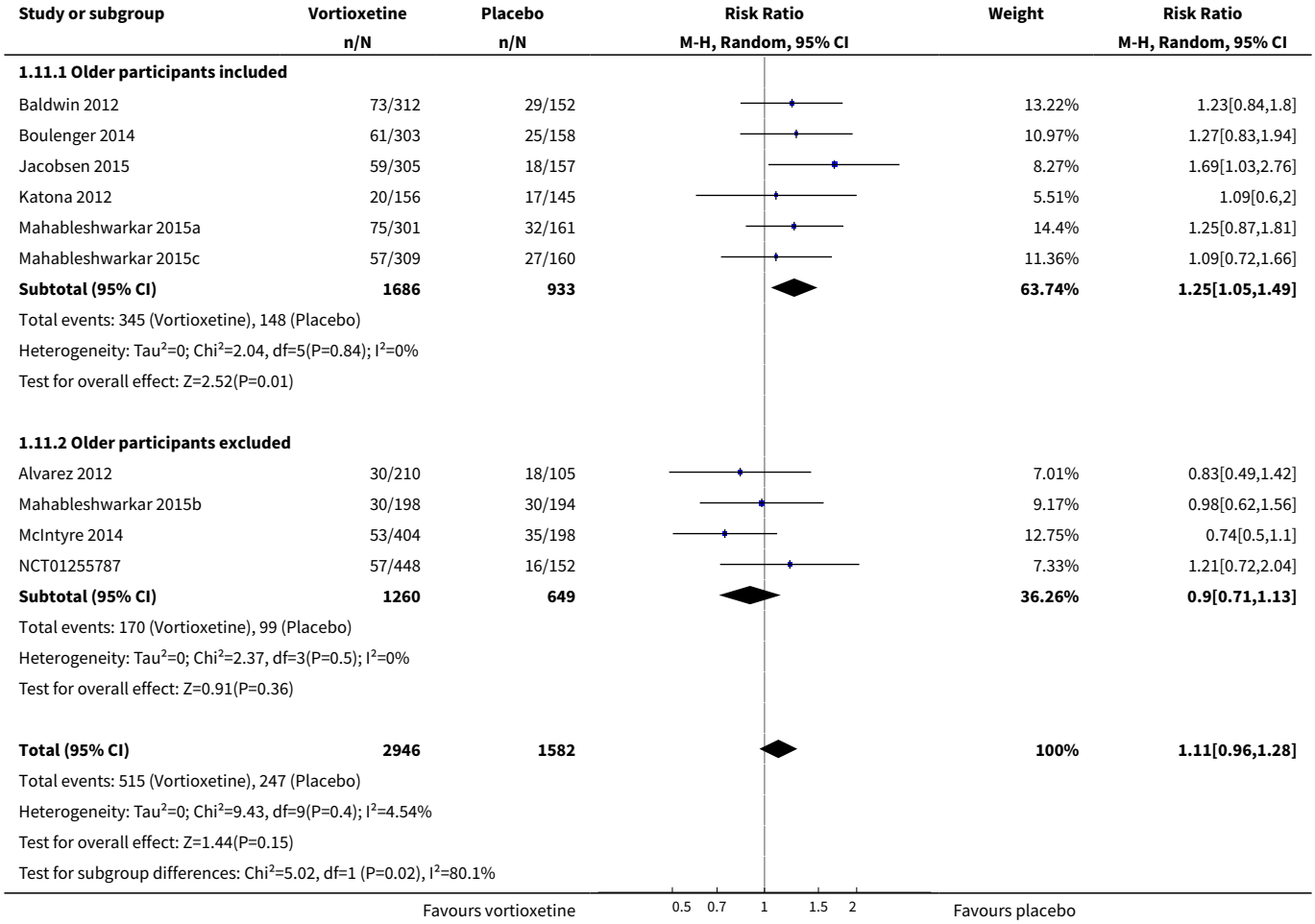


Analysis 1.10. Comparison 1 Vortioxetine versus placebo, Outcome 10 Subgroup analysis: inclusion of older (aged > 65 years) participants - response.



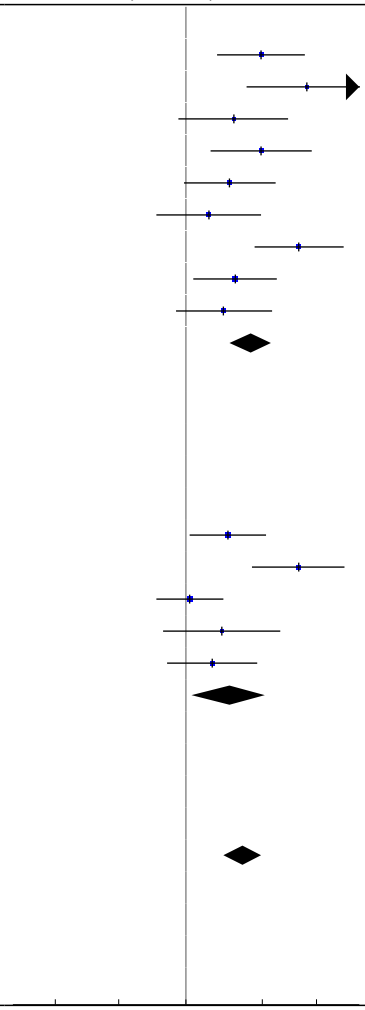


Analysis 1.11. Comparison 1 Vortioxetine versus placebo, Outcome 11 Subgroup analysis: inclusion of older (aged > 65 years) participants - total number of dropouts.



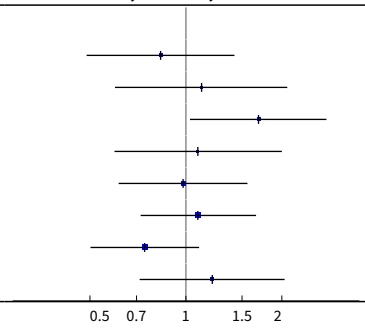
Analysis 1.12. Comparison 1 Vortioxetine versus placebo, Outcome 12 Sensitivity analysis - exclusion > 20% dropouts - response.

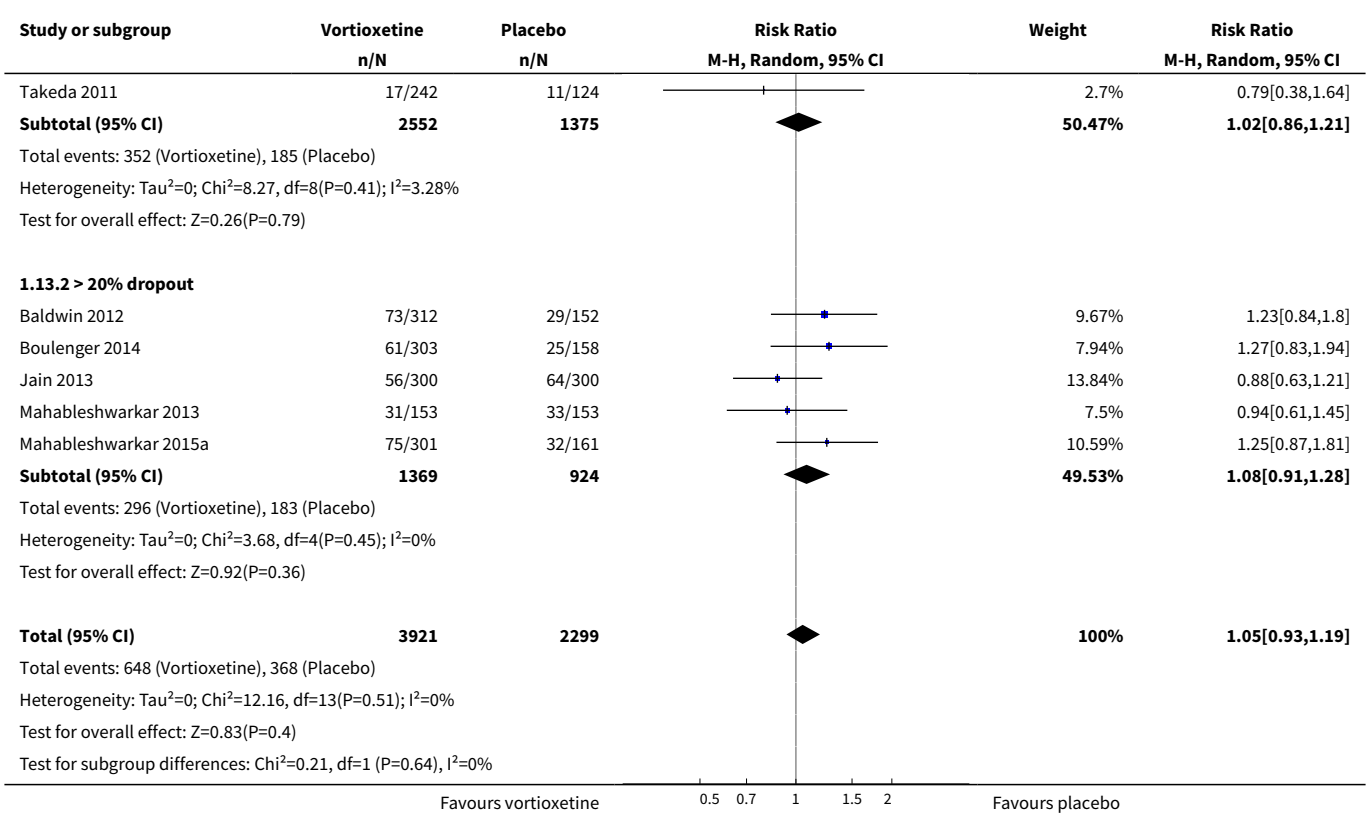
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 < 20% dropouts					
Alvarez 2012	140/210	47/105		7.55%	1.49[1.18,1.88]
Henigsberg 2012	129/280	34/140		5.65%	1.9[1.38,2.61]
Jacobsen 2015	110/305	44/157		6.19%	1.29[0.96,1.72]
Katona 2012	82/156	51/145		6.75%	1.49[1.14,1.95]
Mahableshwarkar 2015b	89/198	69/194		7.27%	1.26[0.99,1.61]
Mahableshwarkar 2015c	107/309	49/160		6.47%	1.13[0.86,1.49]
McIntyre 2014	212/404	57/198		7.42%	1.82[1.44,2.31]
NCT01255787	226/448	59/152		7.88%	1.3[1.04,1.62]
Takeda 2011	117/242	49/124		7.04%	1.22[0.95,1.58]
Subtotal (95% CI)	**2552**	**1375**		**62.23%**	**1.41[1.26,1.57]**
Total events: 1212 (Vortioxetine), 459 (Placebo)					
Heterogeneity: Tau^2=0.01; Chi^2=13.53, df=8(P=0.09); I^2=40.87%					
Test for overall effect: Z=6.01(P<0.0001)					
1.12.2 > 20% dropouts					
Baldwin 2012	174/312	68/152		8.33%	1.25[1.02,1.53]
Boulenger 2014	178/303	51/158		7.26%	1.82[1.42,2.32]
Jain 2013	135/300	132/300		8.96%	1.02[0.86,1.22]
Mahableshwarkar 2013	58/153	48/153		5.83%	1.21[0.89,1.65]
Mahableshwarkar 2015a	129/301	60/161		7.39%	1.15[0.91,1.46]
Subtotal (95% CI)	**1369**	**924**		**37.77%**	**1.26[1.03,1.52]**
Total events: 674 (Vortioxetine), 359 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=14.36, df=4(P=0.01); I^2=72.14%					
Test for overall effect: Z=2.3(P=0.02)					
Total (95% CI)	**3921**	**2299**		**100%**	**1.35[1.22,1.49]**
Total events: 1886 (Vortioxetine), 818 (Placebo)					
Heterogeneity: Tau^2=0.02; Chi^2=32.11, df=13(P=0); I^2=59.51%					
Test for overall effect: Z=5.66(P<0.0001)					
Test for subgroup differences: Chi^2=1, df=1 (P=0.32), I^2=0.04%					



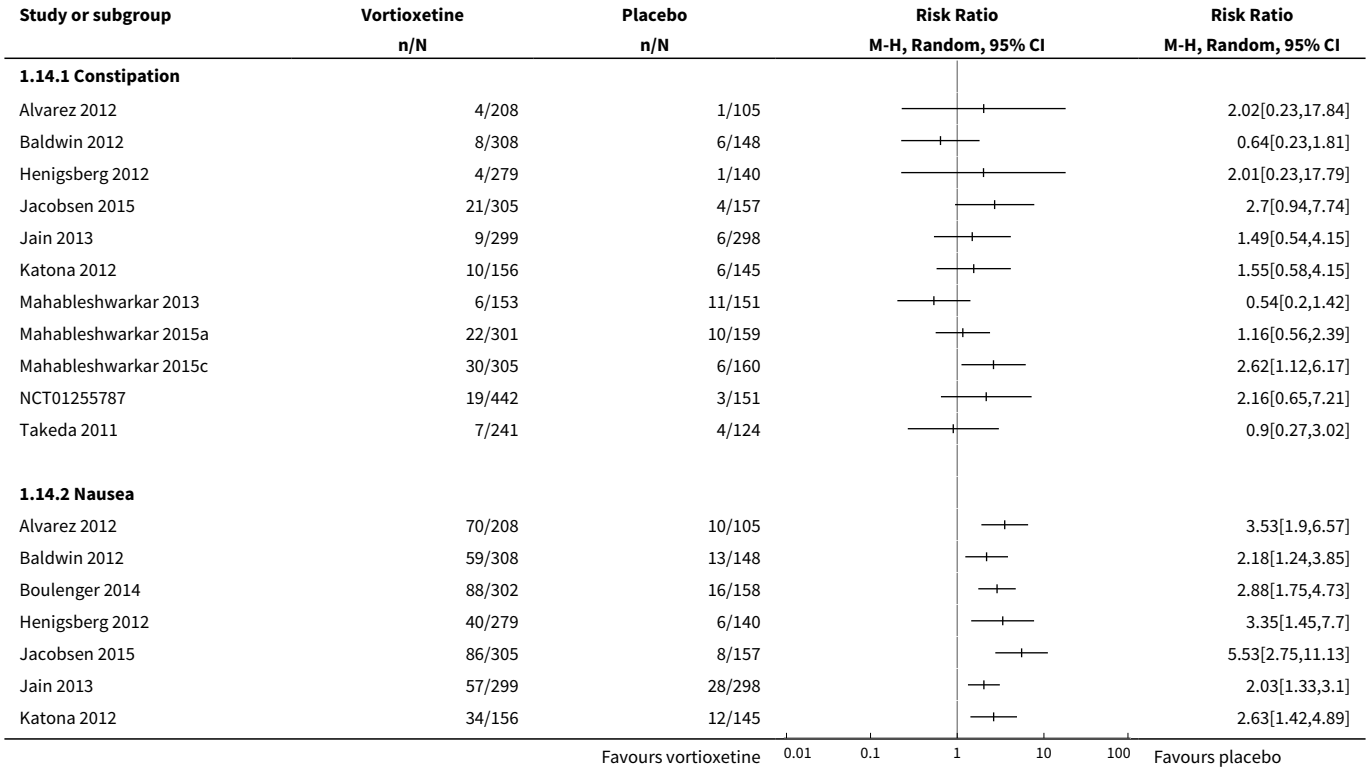
Analysis 1.13. Comparison 1 Vortioxetine versus placebo, Outcome 13 Sensitivity analysis - exclusion > 20% dropouts - total number of dropouts.

Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 < 20% dropout					
Alvarez 2012	30/210	18/105		4.98%	0.83[0.49,1.42]
Henigsberg 2012	29/280	13/140		3.69%	1.12[0.6,2.08]
Jacobsen 2015	59/305	18/157		5.9%	1.69[1.03,2.76]
Katona 2012	20/156	17/145		3.89%	1.09[0.6,2]
Mahableshwarkar 2015b	30/198	30/194		6.57%	0.98[0.62,1.56]
Mahableshwarkar 2015c	57/309	27/160		8.23%	1.09[0.72,1.66]
McIntyre 2014	53/404	35/198		9.3%	0.74[0.5,1.1]
NCT01255787	57/448	16/152		5.21%	1.21[0.72,2.04]

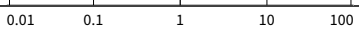




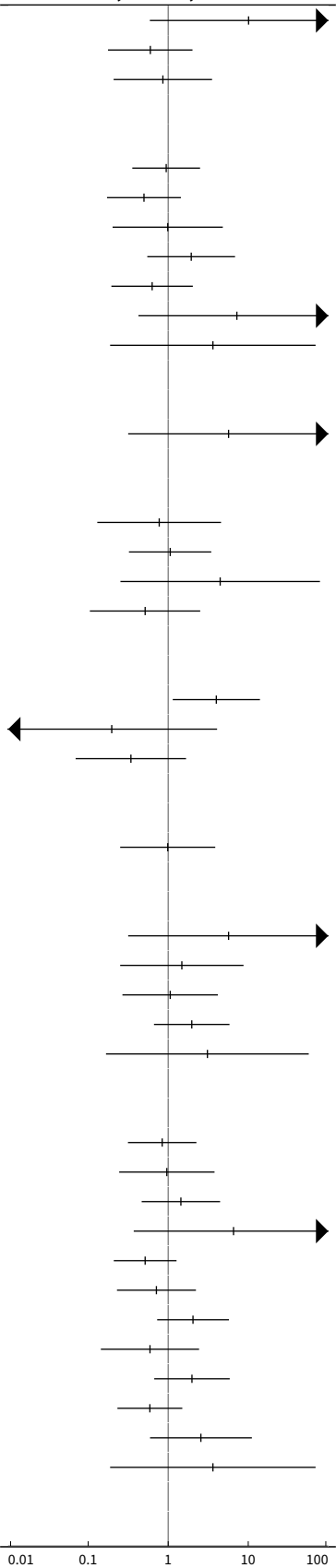
Analysis 1.14. Comparison 1 Vortioxetine versus placebo, Outcome 14 Adverse events.

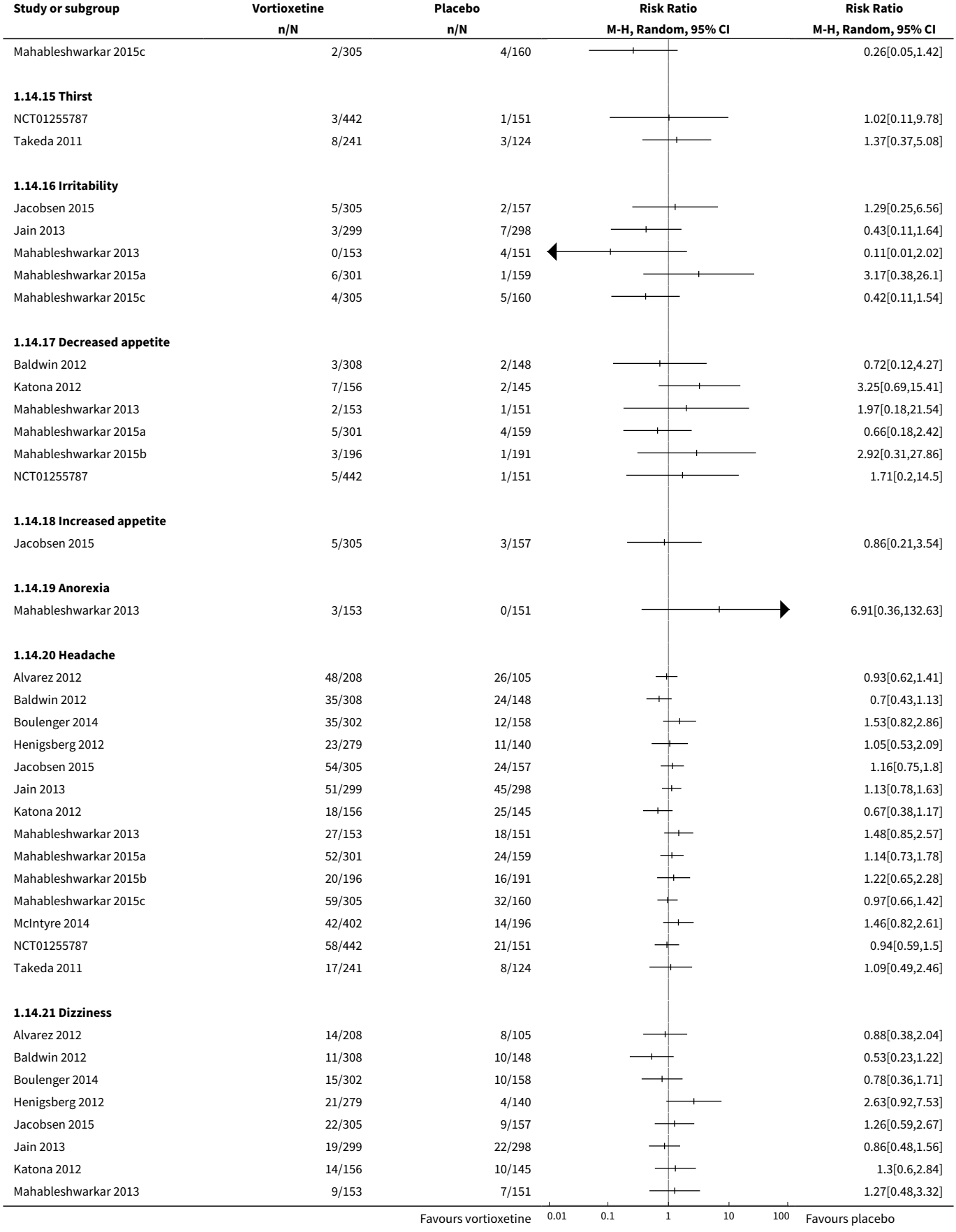


Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2013	44/153	16/151		2.71[1.6,4.59]
Mahableshwarkar 2015a	103/301	18/159		3.02[1.9,4.8]
Mahableshwarkar 2015b	40/196	8/191		4.87[2.34,10.14]
Mahableshwarkar 2015c	98/305	17/160		3.02[1.87,4.88]
McIntyre 2014	75/402	8/196		4.57[2.25,9.29]
NCT01255787	90/442	11/151		2.8[1.54,5.08]
Takeda 2011	55/241	9/124		3.14[1.61,6.15]
1.14.3 Diarrhoea				
Alvarez 2012	16/208	5/105		1.62[0.61,4.29]
Baldwin 2012	11/308	10/148		0.53[0.23,1.22]
Boulenger 2014	17/302	6/158		1.48[0.6,3.68]
Henigsberg 2012	7/279	2/140		1.76[0.37,8.34]
Jacobsen 2015	31/305	14/157		1.14[0.62,2.08]
Jain 2013	34/299	21/298		1.61[0.96,2.71]
Katona 2012	8/156	10/145		0.74[0.3,1.83]
Mahableshwarkar 2013	14/153	13/151		1.06[0.52,2.18]
Mahableshwarkar 2015a	34/301	10/159		1.8[0.91,3.54]
Mahableshwarkar 2015b	11/196	5/191		2.14[0.76,6.05]
Mahableshwarkar 2015c	25/305	10/160		1.31[0.65,2.66]
NCT01255787	18/442	14/151		0.44[0.22,0.86]
Takeda 2011	23/241	10/124		1.18[0.58,2.41]
1.14.4 Dry mouth				
Alvarez 2012	16/208	7/105		1.15[0.49,2.72]
Baldwin 2012	15/308	11/148		0.66[0.31,1.39]
Boulenger 2014	14/302	5/158		1.46[0.54,3.99]
Henigsberg 2012	6/279	3/140		1[0.25,3.95]
Jacobsen 2015	14/305	15/157		0.48[0.24,0.97]
Jain 2013	25/299	19/298		1.31[0.74,2.33]
Katona 2012	10/156	7/145		1.33[0.52,3.4]
Mahableshwarkar 2013	16/153	11/151		1.44[0.69,2.99]
Mahableshwarkar 2015a	36/301	16/159		1.19[0.68,2.07]
Mahableshwarkar 2015b	6/196	9/191		0.65[0.24,1.79]
Mahableshwarkar 2015c	32/305	11/160		1.53[0.79,2.95]
NCT01255787	18/442	3/151		2.05[0.61,6.86]
1.14.5 Vomiting				
Alvarez 2012	11/208	1/105		5.55[0.73,42.43]
Baldwin 2012	13/308	5/148		1.25[0.45,3.44]
Jacobsen 2015	17/305	3/157		2.92[0.87,9.8]
Jain 2013	8/299	4/298		1.99[0.61,6.55]
Mahableshwarkar 2013	7/153	1/151		6.91[0.86,55.48]
Mahableshwarkar 2015a	20/301	1/159		10.56[1.43,78]
Mahableshwarkar 2015c	25/305	4/160		3.28[1.16,9.26]
NCT01255787	9/442	3/151		1.02[0.28,3.74]
Takeda 2011	6/241	3/124		1.03[0.26,4.05]
1.14.6 Abdominal pain upper				
Henigsberg 2012	2/279	5/140		0.2[0.04,1.02]
Jacobsen 2015	4/305	3/157		0.69[0.16,3.03]
Mahableshwarkar 2013	6/153	2/151		2.96[0.61,14.44]

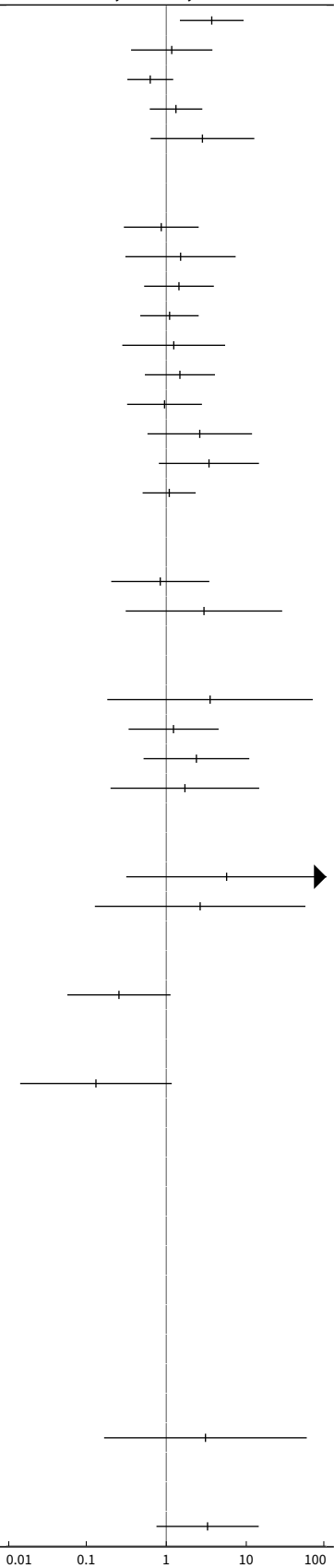


Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2015a	9/301	0/159		10.07[0.59,171.84]
NCT01255787	7/442	4/151		0.6[0.18,2.01]
Takeda 2011	5/241	3/124		0.86[0.21,3.53]
1.14.7 Dyspepsia				
Jacobsen 2015	11/305	6/157		0.94[0.36,2.5]
Jain 2013	5/299	10/298		0.5[0.17,1.44]
Mahableshwarkar 2013	3/153	3/151		0.99[0.2,4.81]
Mahableshwarkar 2015a	11/301	3/159		1.94[0.55,6.84]
Mahableshwarkar 2015c	6/305	5/160		0.63[0.2,2.03]
NCT01255787	10/442	0/151		7.21[0.42,122.23]
Takeda 2011	3/241	0/124		3.62[0.19,69.45]
1.14.8 Gastro-oesophageal reflux disease				
Jacobsen 2015	5/305	0/157		5.68[0.32,102.06]
1.14.9 Abdominal discomfort				
Jacobsen 2015	3/305	2/157		0.77[0.13,4.57]
Mahableshwarkar 2015a	8/301	4/159		1.06[0.32,3.45]
NCT01255787	6/442	0/151		4.46[0.25,78.71]
Takeda 2011	3/241	3/124		0.51[0.11,2.51]
1.14.10 Abdominal pain				
Jain 2013	12/299	3/298		3.99[1.14,13.98]
Mahableshwarkar 2013	0/153	2/151		0.2[0.01,4.08]
NCT01255787	3/442	3/151		0.34[0.07,1.67]
1.14.11 Stomach discomfort				
Mahableshwarkar 2013	4/153	4/151		0.99[0.25,3.87]
1.14.12 Flatulence				
Jacobsen 2015	5/305	0/157		5.68[0.32,102.06]
Mahableshwarkar 2013	3/153	2/151		1.48[0.25,8.73]
Mahableshwarkar 2015a	6/301	3/159		1.06[0.27,4.17]
Mahableshwarkar 2015c	15/305	4/160		1.97[0.66,5.83]
NCT01255787	4/442	0/151		3.09[0.17,57.02]
1.14.13 Fatigue				
Alvarez 2012	10/208	6/105		0.84[0.31,2.25]
Baldwin 2012	6/308	3/148		0.96[0.24,3.79]
Boulenger 2014	11/302	4/158		1.44[0.47,4.45]
Henigsberg 2012	6/279	0/140		6.55[0.37,115.38]
Jacobsen 2015	9/305	9/157		0.51[0.21,1.27]
Jain 2013	5/299	7/298		0.71[0.23,2.22]
Katona 2012	11/156	5/145		2.04[0.73,5.74]
Mahableshwarkar 2013	3/153	5/151		0.59[0.14,2.43]
Mahableshwarkar 2015a	15/301	4/159		1.98[0.67,5.87]
Mahableshwarkar 2015c	9/305	8/160		0.59[0.23,1.5]
NCT01255787	15/442	2/151		2.56[0.59,11.07]
Takeda 2011	3/241	0/124		3.62[0.19,69.45]
1.14.14 Pain				





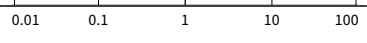
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2015a	35/301	5/159		3.7[1.48,9.25]
Mahableshwarkar 2015b	6/196	5/191		1.17[0.36,3.77]
Mahableshwarkar 2015c	18/305	15/160		0.63[0.33,1.22]
NCT01255787	31/442	8/151		1.32[0.62,2.82]
Takeda 2011	11/241	2/124		2.83[0.64,12.57]
1.14.22 Somnolence				
Baldwin 2012	9/308	5/148		0.86[0.3,2.54]
Henigsberg 2012	6/279	2/140		1.51[0.31,7.36]
Jacobsen 2015	14/305	5/157		1.44[0.53,3.93]
Jain 2013	11/299	10/298		1.1[0.47,2.54]
Katona 2012	4/156	3/145		1.24[0.28,5.44]
Mahableshwarkar 2013	9/153	6/151		1.48[0.54,4.06]
Mahableshwarkar 2015a	9/301	5/159		0.95[0.32,2.79]
Mahableshwarkar 2015c	10/305	2/160		2.62[0.58,11.83]
NCT01255787	20/442	2/151		3.42[0.81,14.44]
Takeda 2011	19/241	9/124		1.09[0.51,2.33]
1.14.23 Tremor				
Alvarez 2012	5/208	3/105		0.84[0.21,3.45]
Mahableshwarkar 2013	3/153	1/151		2.96[0.31,28.15]
1.14.24 Sedation				
Henigsberg 2012	3/279	0/140		3.53[0.18,67.77]
Mahableshwarkar 2013	5/153	4/151		1.23[0.34,4.51]
Mahableshwarkar 2015a	9/301	2/159		2.38[0.52,10.87]
NCT01255787	5/442	1/151		1.71[0.2,14.5]
1.14.25 Dysgeusia				
Jacobsen 2015	5/305	0/157		5.68[0.32,102.06]
Mahableshwarkar 2015a	2/301	0/159		2.65[0.13,54.84]
1.14.26 Hypoaesthesia				
NCT01255787	3/442	4/151		0.26[0.06,1.13]
1.14.27 Poor-quality sleep				
Mahableshwarkar 2015a	1/301	4/159		0.13[0.01,1.17]
1.14.28 Ejaculation delayed (men)				
Alvarez 2012	0/73	0/36		Not estimable
Katona 2012	0/49	0/55		Not estimable
1.14.29 Erectile dysfunction (men)				
Alvarez 2012	0/73	0/36		Not estimable
Katona 2012	0/49	0/55		Not estimable
Mahableshwarkar 2015a	0/301	0/159		Not estimable
1.14.30 Dysmenorrhoea				
NCT01255787	4/442	0/151		3.09[0.17,57.02]
1.14.31 Hyperhidrosis				
Alvarez 2012	13/208	2/105		3.28[0.75,14.27]



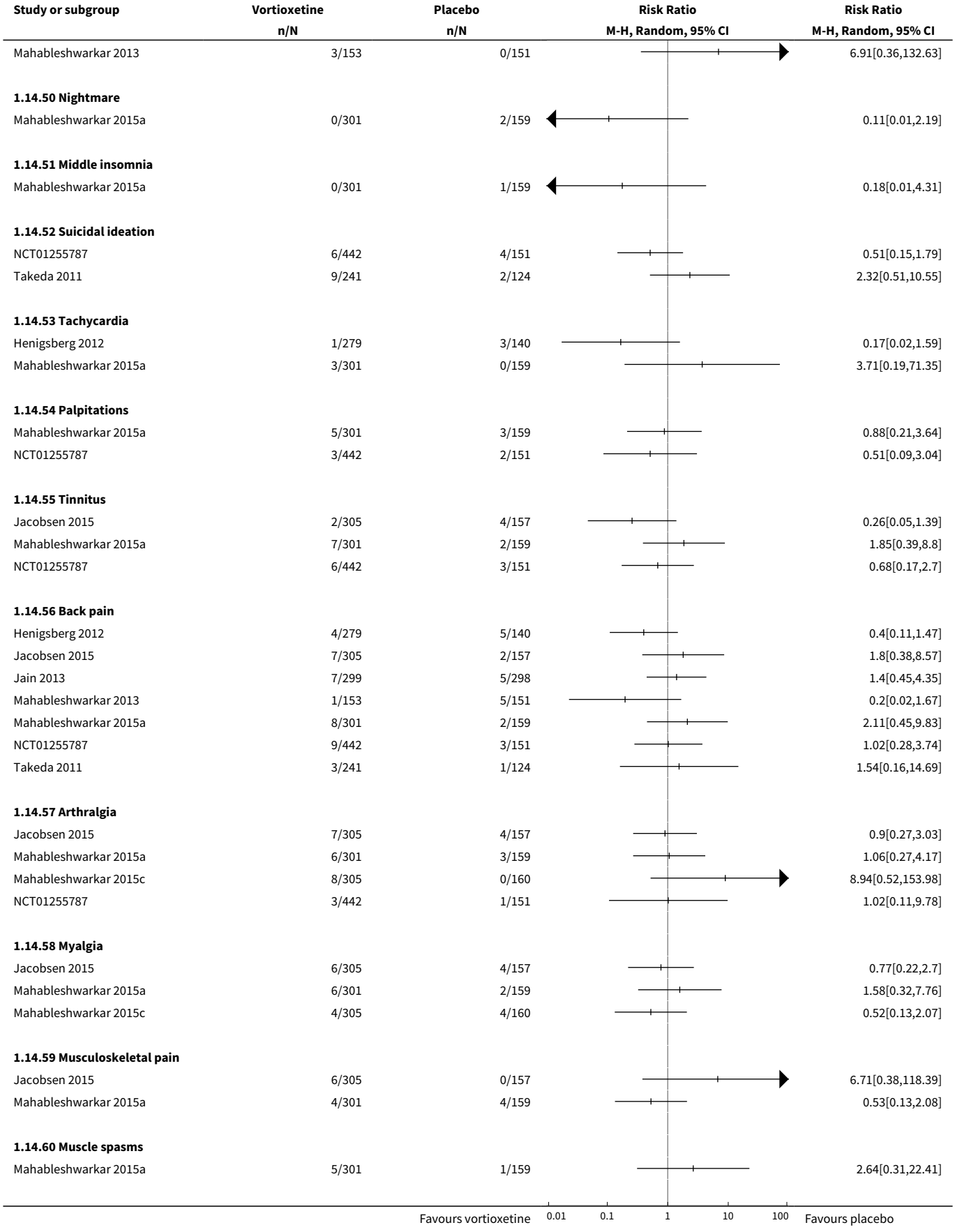
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baldwin 2012	8/308	1/148		3.84[0.49,30.45]
Boulenger 2014	5/302	6/158		0.44[0.14,1.41]
Henigsberg 2012	5/279	1/140		2.51[0.3,21.27]
Jain 2013	4/299	7/298		0.57[0.17,1.93]
Katona 2012	6/156	4/145		1.39[0.4,4.84]
Mahableshwarkar 2013	4/153	4/151		0.99[0.25,3.87]
Mahableshwarkar 2015a	4/301	3/159		0.7[0.16,3.11]
NCT01255787	12/442	2/151		2.05[0.46,9.05]
1.14.32 Pruritus generalised				
Jacobsen 2015	9/305	3/157		1.54[0.42,5.62]
NCT01255787	5/442	0/151		3.77[0.21,67.86]
1.14.33 Pruritus				
Jacobsen 2015	5/305	1/157		2.57[0.3,21.84]
1.14.34 Vision blurred				
Alvarez 2012	3/208	2/105		0.76[0.13,4.46]
Jacobsen 2015	3/305	4/157		0.39[0.09,1.7]
Mahableshwarkar 2013	1/153	3/151		0.33[0.03,3.13]
Mahableshwarkar 2015a	4/301	2/159		1.06[0.2,5.71]
Mahableshwarkar 2015c	5/305	1/160		2.62[0.31,22.26]
1.14.35 Nasopharyngitis				
Alvarez 2012	15/208	9/105		0.84[0.38,1.86]
Baldwin 2012	15/308	6/148		1.2[0.48,3.03]
Henigsberg 2012	10/279	8/140		0.63[0.25,1.55]
Jacobsen 2015	11/305	1/157		5.66[0.74,43.46]
Jain 2013	7/299	5/298		1.4[0.45,4.35]
Mahableshwarkar 2015a	15/301	10/159		0.79[0.36,1.72]
Mahableshwarkar 2015b	7/196	11/191		0.62[0.25,1.57]
Mahableshwarkar 2015c	9/305	8/160		0.59[0.23,1.5]
McIntyre 2014	16/402	10/196		0.78[0.36,1.69]
NCT01255787	63/442	18/151		1.2[0.73,1.95]
Takeda 2011	41/241	21/124		1[0.62,1.62]
1.14.36 Influenza				
Henigsberg 2012	7/279	2/140		1.76[0.37,8.34]
Mahableshwarkar 2015c	4/305	7/160		0.3[0.09,1.01]
1.14.37 Respiratory tract infection				
Jacobsen 2015	24/305	15/157		0.82[0.44,1.52]
Jain 2013	3/299	6/298		0.5[0.13,1.97]
Mahableshwarkar 2013	2/153	3/151		0.66[0.11,3.88]
Mahableshwarkar 2015a	17/301	15/159		0.6[0.31,1.17]
Mahableshwarkar 2015c	13/305	12/160		0.57[0.27,1.22]
NCT01255787	4/442	0/151		3.09[0.17,57.02]
1.14.38 Gastroenteritis viral				
Jacobsen 2015	7/305	3/157		1.2[0.31,4.58]
Mahableshwarkar 2015a	5/301	3/159		0.88[0.21,3.64]
Takeda 2011	0/241	3/124		0.07[0,1.42]

Favours vortioxetine — Favours placebo

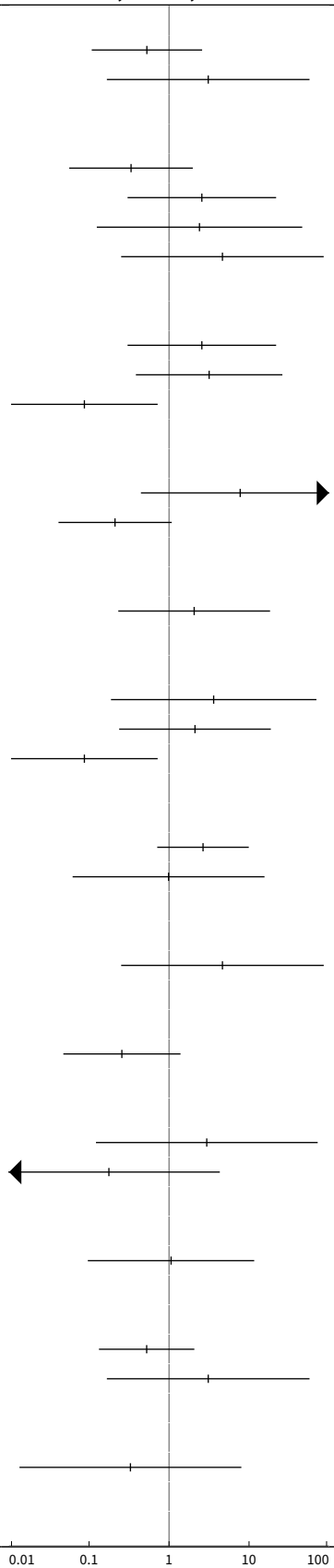
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.14.39 Sinusitis				
Jacobsen 2015	5/305	0/157		5.68[0.32,102.06]
1.14.40 Urinary tract infection				
Jain 2013	6/299	5/298		1.2[0.37,3.88]
Mahableshwarkar 2015a	4/301	0/159		4.77[0.26,88.01]
1.14.41 Bronchitis				
Mahableshwarkar 2015c	2/305	4/160		0.26[0.05,1.42]
NCT01255787	3/442	3/151		0.34[0.07,1.67]
1.14.42 Anorgasmia				
Alvarez 2012	0/208	0/105		Not estimable
1.14.43 Insomnia				
Alvarez 2012	13/208	5/105		1.31[0.48,3.58]
Baldwin 2012	14/308	6/148		1.12[0.44,2.86]
Jacobsen 2015	9/305	6/157		0.77[0.28,2.13]
Jain 2013	12/299	13/298		0.92[0.43,1.98]
Mahableshwarkar 2013	6/153	6/151		0.99[0.33,2.99]
Mahableshwarkar 2015a	18/301	8/159		1.19[0.53,2.67]
Mahableshwarkar 2015c	10/305	4/160		1.31[0.42,4.12]
NCT01255787	17/442	2/151		2.9[0.68,12.42]
Takeda 2011	4/241	1/124		2.06[0.23,18.22]
1.14.44 Restlessness				
Henigsberg 2012	5/279	1/140		2.51[0.3,21.27]
Mahableshwarkar 2013	5/153	1/151		4.93[0.58,41.74]
Mahableshwarkar 2015a	5/301	4/159		0.66[0.18,2.42]
1.14.45 Abnormal dreams				
Jacobsen 2015	10/305	2/157		2.57[0.57,11.6]
Mahableshwarkar 2015a	13/301	7/159		0.98[0.4,2.41]
1.14.46 Anxiety				
Jacobsen 2015	2/305	4/157		0.26[0.05,1.39]
Mahableshwarkar 2013	5/153	2/151		2.47[0.49,12.52]
Mahableshwarkar 2015a	6/301	4/159		0.79[0.23,2.77]
Mahableshwarkar 2015c	5/305	1/160		2.62[0.31,22.26]
1.14.47 Depression				
Jain 2013	7/299	5/298		1.4[0.45,4.35]
Mahableshwarkar 2015a	0/301	4/159		0.06[0,1.09]
NCT01255787	4/442	3/151		0.46[0.1,2.01]
1.14.48 Libido decreased				
Mahableshwarkar 2013	3/153	3/151		0.99[0.2,4.81]
Mahableshwarkar 2015a	6/301	3/159		1.06[0.27,4.17]
NCT01255787	3/442	0/151		2.4[0.12,46.23]
1.14.49 Orgasm abnormal				



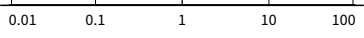
Favours vortioxetine — Favours placebo



Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.14.61 Pain in extremity				
Mahableshwarkar 2015a	3/301	3/159		0.53[0.11,2.59]
NCT01255787	4/442	0/151		3.09[0.17,57.02]
1.14.62 Hypertension				
Henigsberg 2012	2/279	3/140		0.33[0.06,1.98]
Jacobsen 2015	5/305	1/157		2.57[0.3,21.84]
NCT01255787	3/442	0/151		2.4[0.12,46.23]
Takeda 2011	4/241	0/124		4.65[0.25,85.66]
1.14.63 Hot flush				
Jacobsen 2015	5/305	1/157		2.57[0.3,21.84]
Mahableshwarkar 2015a	6/301	1/159		3.17[0.38,26.1]
Mahableshwarkar 2015c	1/305	6/160		0.09[0.01,0.72]
1.14.64 Fall				
Jacobsen 2015	7/305	0/157		7.75[0.45,134.74]
Mahableshwarkar 2015a	2/301	5/159		0.21[0.04,1.08]
1.14.65 Ligament sprain				
Jacobsen 2015	4/305	1/157		2.06[0.23,18.27]
1.14.66 Muscle strain				
Jacobsen 2015	3/305	0/157		3.61[0.19,69.54]
Mahableshwarkar 2015a	4/301	1/159		2.11[0.24,18.75]
Mahableshwarkar 2015c	1/305	6/160		0.09[0.01,0.72]
1.14.67 Accidental overdose				
Jain 2013	8/299	3/298		2.66[0.71,9.92]
Mahableshwarkar 2013	1/153	1/151		0.99[0.06,15.64]
1.14.68 Road traffic accident				
Jacobsen 2015	4/305	0/157		4.65[0.25,85.77]
1.14.69 Nasal congestion				
Jacobsen 2015	2/305	4/157		0.26[0.05,1.39]
1.14.70 Yawning				
Mahableshwarkar 2013	1/153	0/151		2.96[0.12,72.12]
Mahableshwarkar 2015a	0/301	1/159		0.18[0.01,4.31]
1.14.71 Rhinorrhoea				
Mahableshwarkar 2015a	2/301	1/159		1.06[0.1,11.56]
1.14.72 Oropharyngeal pain				
Mahableshwarkar 2015c	4/305	4/160		0.52[0.13,2.07]
NCT01255787	4/442	0/151		3.09[0.17,57.02]
1.14.73 Weight decreased				
Mahableshwarkar 2013	0/153	1/151		0.33[0.01,8.01]
1.14.74 Blood pressure increased				

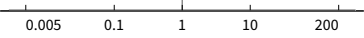


Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2013	1/153	1/151		0.99[0.06,15.64]
1.14.75 Hepatic function abnormal				
NCT01255787	3/442	0/151		2.4[0.12,46.23]

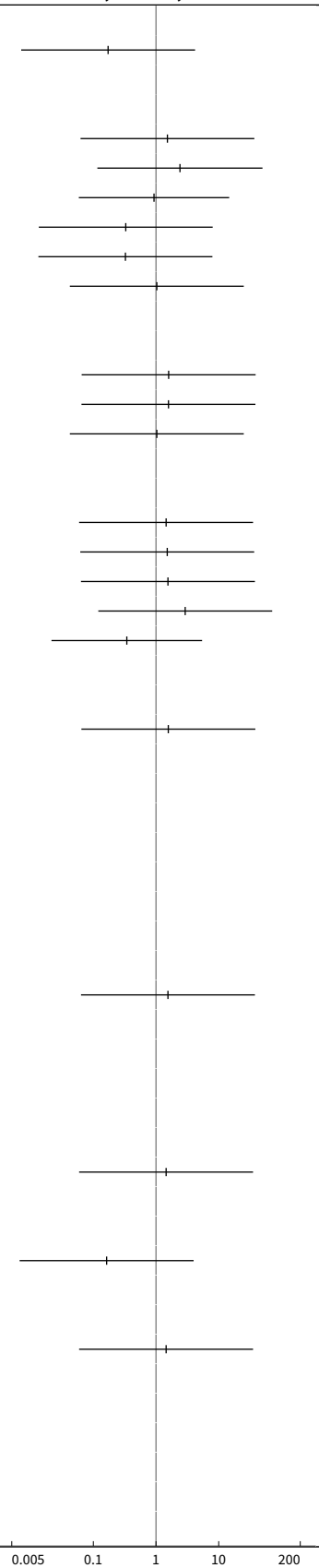


Analysis 1.15. Comparison 1 Vortioxetine versus placebo, Outcome 15 Serious adverse events.

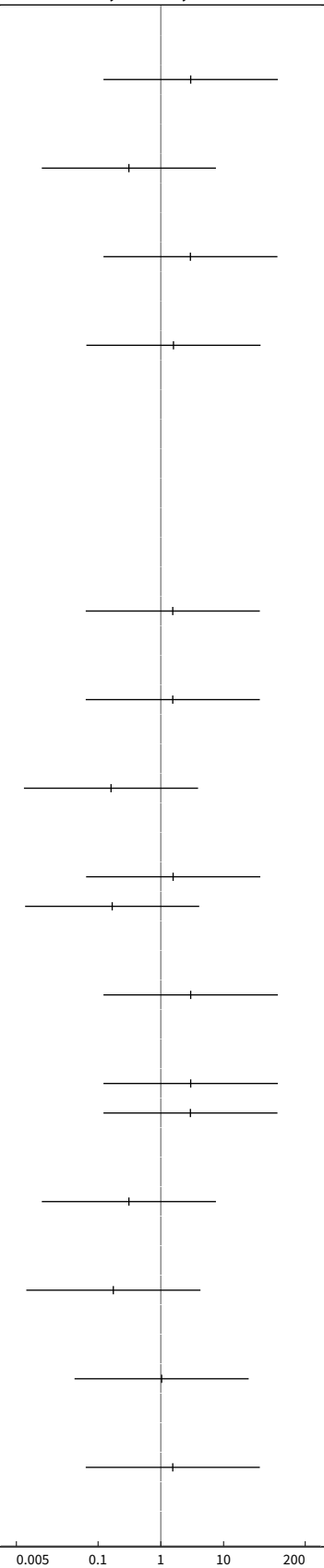
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.15.1 Varicella zoster infection				
Alvarez 2012	1/208	0/105		1.52[0.06,37.03]
1.15.2 Kidney infection				
Jacobsen 2015	1/305	0/157		1.55[0.06,37.81]
1.15.3 Herpes zoster infection				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.4 Puncture site infection				
Jain 2013	0/299	1/298		0.33[0.01,8.12]
1.15.5 Gastroenteritis				
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.6 Pyelonephritis				
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.7 Brain tumour				
Alvarez 2012	0/208	0/105		Not estimable
1.15.8 Gallbladder cancer				
Baldwin 2012	1/308	0/148		1.45[0.06,35.3]
1.15.9 Colon cancer				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.10 Laryngeal cancer				
Jain 2013	0/299	1/298		0.33[0.01,8.12]
1.15.11 Renal cell carcinoma				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.12 Bile duct cancer				
Katona 2012	0/156	1/145		0.31[0.01,7.55]
1.15.13 Prostate cancer				
Katona 2012	0/49	0/55		Not estimable



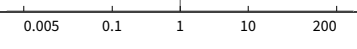
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.15.14 Breast cancer recurrent				
Takeda 2011	0/241	1/124		0.17[0.01,4.2]
1.15.15 Worsening of major depressive disorder				
Alvarez 2012	1/208	0/105		1.52[0.06,37.03]
Baldwin 2012	2/308	0/148		2.41[0.12,49.9]
Katona 2012	1/156	1/145		0.93[0.06,14.72]
Mahableshwarkar 2013	0/153	1/151		0.33[0.01,8.01]
Mahableshwarkar 2015b	0/196	1/191		0.32[0.01,7.93]
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.16 Suicidal ideation				
Mahableshwarkar 2015a	1/301	0/159		1.59[0.07,38.79]
Mahableshwarkar 2015c	1/305	0/160		1.58[0.06,38.53]
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.17 Suicide attempt				
Baldwin 2012	1/308	0/148		1.45[0.06,35.3]
Henigsberg 2012	1/279	0/140		1.51[0.06,36.85]
Jacobsen 2015	1/305	0/157		1.55[0.06,37.81]
Mahableshwarkar 2015b	1/196	0/191		2.92[0.12,71.33]
NCT01255787	1/442	1/151		0.34[0.02,5.43]
1.15.18 Intentional self-injury				
Boulenger 2014	1/302	0/158		1.57[0.06,38.42]
1.15.19 Self-injurious behaviour				
Boulenger 2014	0/302	0/158		Not estimable
1.15.20 Panic attack				
Mahableshwarkar 2013	0/153	0/151		Not estimable
1.15.21 Suicidal behaviour				
Takeda 2011	1/241	0/124		1.55[0.06,37.76]
1.15.22 Middle ear effusion				
Baldwin 2012	0/308	0/148		Not estimable
1.15.23 Jaundice cholestatic				
Baldwin 2012	1/308	0/148		1.45[0.06,35.3]
1.15.24 Cholecystitis				
McIntyre 2014	0/402	1/196		0.16[0.01,3.98]
1.15.25 Pelvic fracture				
Baldwin 2012	1/308	0/148		1.45[0.06,35.3]
1.15.26 Intentional overdose				
Boulenger 2014	0/302	0/158		Not estimable
1.15.27 Lumbar vertebral fracture				
Boulenger 2014	0/302	0/158		Not estimable



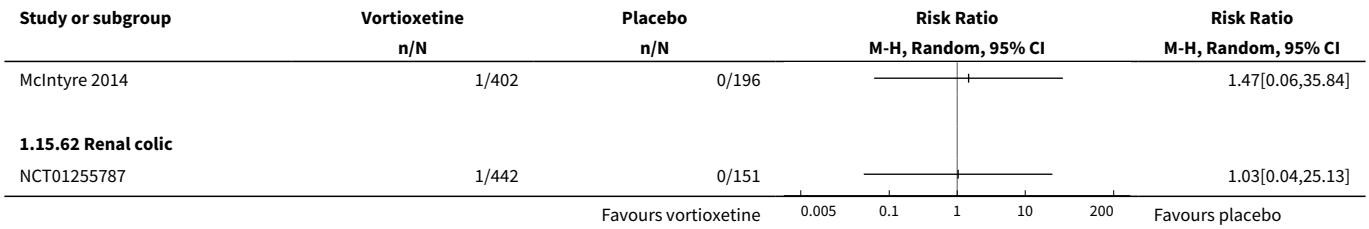
Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.15.28 Injury				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.29 Hip fracture				
Katona 2012	0/156	1/145		0.31[0.01,7.55]
1.15.30 Head injury				
Mahableshwarkar 2013	1/153	0/151		2.96[0.12,72.12]
1.15.31 Stress fracture				
Mahableshwarkar 2015a	1/301	0/159		1.59[0.07,38.79]
1.15.32 Craniocerebral injury				
Mahableshwarkar 2015b	0/196	0/191		Not estimable
1.15.33 Subdural haematoma				
Mahableshwarkar 2015b	0/196	0/191		Not estimable
1.15.34 Brain contusion				
Takeda 2011	1/241	0/124		1.55[0.06,37.76]
1.15.35 Road traffic accident				
Takeda 2011	1/241	0/124		1.55[0.06,37.76]
1.15.36 Serotonin syndrome				
Baldwin 2012	0/308	1/148		0.16[0.01,3.92]
1.15.37 Dizziness				
Boulenger 2014	1/302	0/158		1.57[0.06,38.42]
Henigsberg 2012	0/279	1/140		0.17[0.01,4.09]
1.15.38 Cerebrovascular accident				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.39 Convulsion				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
Mahableshwarkar 2013	1/153	0/151		2.96[0.12,72.12]
1.15.40 Transient ischaemic attack				
Katona 2012	0/156	1/145		0.31[0.01,7.55]
1.15.41 Lumbar radiculopathy				
Mahableshwarkar 2015c	0/305	1/160		0.18[0.01,4.28]
1.15.42 Syncope				
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.43 Cerebral haematoma				
Takeda 2011	1/241	0/124		1.55[0.06,37.76]
1.15.44 Subarachnoid haemorrhage				



Study or subgroup	Vortioxetine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Takeda 2011	1/241	0/124		1.55[0.06,37.76]
1.15.45 Adenomyosis				
Baldwin 2012	0/204	1/103		0.17[0.01,4.12]
1.15.46 Vaginal haemorrhage				
Boulenger 2014	0/188	0/110		Not estimable
1.15.47 Pulmonary embolism				
Baldwin 2012	0/308	1/148		0.16[0.01,3.92]
1.15.48 Blood pressure decreased				
Boulenger 2014	1/302	0/158		1.57[0.06,38.42]
1.15.49 Tachycardia				
Henigsberg 2012	1/279	0/140		1.51[0.06,36.85]
1.15.50 Acute myocardial infarction				
Mahableshwarkar 2013	0/153	0/151		Not estimable
Mahableshwarkar 2015b	0/196	1/191		0.32[0.01,7.93]
1.15.51 Atrial fibrillation				
Mahableshwarkar 2013	1/153	0/151		2.96[0.12,72.12]
1.15.52 Coronary artery disease				
Mahableshwarkar 2013	1/153	0/151		2.96[0.12,72.12]
1.15.53 Pancreatitis				
Henigsberg 2012	1/279	1/140		0.5[0.03,7.96]
1.15.54 Hiatus hernia				
McIntyre 2014	0/402	1/196		0.16[0.01,3.98]
1.15.55 Drug hypersensitivity				
Jain 2013	1/299	0/298		2.99[0.12,73.1]
1.15.56 Abortion spontaneous				
Jain 2013	0/299	1/298		0.33[0.01,8.12]
1.15.57 Ectopic pregnancy				
Jain 2013	0/299	1/298		0.33[0.01,8.12]
1.15.58 Abortion missed				
NCT01255787	1/442	0/151		1.03[0.04,25.13]
1.15.59 Abortion induced				
Mahableshwarkar 2013	0/153	1/151		0.33[0.01,8.01]
1.15.60 Type 1 diabetes mellitus				
McIntyre 2014	1/402	0/196		1.47[0.06,35.84]
1.15.61 Hypertension				



Favours vortioxetine Favours placebo



Comparison 2. Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
1.1 Vortioxetine vs venlafaxine	2	767	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.25]
1.2 Vortioxetine vs duloxetine	6	2392	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.79, 0.94]
2 Total number of dropouts	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
2.1 Vortioxetine vs venlafaxine	2	767	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.93]
2.2 Vortioxetine vs duloxetine	6	2392	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.76, 1.21]
3 Remission	8	3155	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.77, 1.03]
3.1 Vortioxetine vs venlafaxine	2	767	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.81, 1.20]
3.2 Vortioxetine vs duloxetine	6	2388	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.02]
4 Depressive symptoms	8	2807	Mean Difference (IV, Random, 95% CI)	1.52 [0.50, 2.53]
4.1 Vortioxetine vs venlafaxine	2	701	Mean Difference (IV, Random, 95% CI)	0.02 [-2.49, 2.54]
4.2 Vortioxetine vs duloxetine	6	2106	Mean Difference (IV, Random, 95% CI)	1.99 [1.15, 2.83]
5 Dropout due to adverse events	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.51, 1.08]
5.1 Vortioxetine vs venlafaxine	2	767	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.26, 0.67]
5.2 Vortioxetine vs duloxetine	6	2392	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.31]
6 Dropout due to inefficacy	8	3159	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.70, 3.30]
6.1 Vortioxetine vs venlafaxine	2	767	Risk Ratio (M-H, Random, 95% CI)	2.68 [0.99, 7.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Vortioxetine vs duloxetine	6	2392	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.41, 3.31]
7 Tolerability	8	3134	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.86, 0.94]
7.1 Vortioxetine vs venlafaxine	2	758	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
7.2 Vortioxetine vs duloxetine	6	2376	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.84, 0.95]
8 Subgroup analysis: fixed vs flexible dosing - response	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
8.1 Fixed dosing	7	2751	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.81, 1.01]
8.2 Flexible dosing	1	408	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.14]
9 Subgroup analysis: fixed vs flexible dosing - total number of dropouts	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
9.1 Fixed dosing	7	2751	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.71, 1.11]
9.2 Flexible dosing	1	408	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.60, 1.47]
10 Subgroup analysis: inclusion of older (aged > 65 years) participants - response	7	2850	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.03]
10.1 Older participants included	4	1675	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.77, 0.98]
10.2 Older participants excluded	3	1175	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.15]
11 Subgroup analysis: inclusion of older (aged > 65 years) participants - total number of dropouts	7	2854	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.74, 1.15]
11.1 Older participants included	4	1679	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.45]
11.2 Older participants excluded	3	1175	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.60, 0.97]
12 Sensitivity analysis - unequal dosing - response	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
12.1 Equal dosing	2	912	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.97, 1.22]
12.2 Vortioxetine dose higher	2	903	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.72, 0.90]
12.3 Vortioxetine dose lower	3	936	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.78, 0.98]
12.4 Flexible vs fixed dosing	1	408	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Sensitivity analysis - unequal dosing - total number of dropouts	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
13.1 Equal dosing	2	912	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.96]
13.2 Vortioxetine dose higher	2	903	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.74, 2.39]
13.3 Vortioxetine dose lower	3	936	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.59, 1.02]
13.4 Flexible vs fixed dosing	1	408	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.60, 1.47]
14 Sensitivity analysis - exclusion > 20% dropouts - response	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
14.1 < 20% dropouts	3	1039	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.01]
14.2 > 20% dropouts	5	2120	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.07]
15 Sensitivity analysis - exclusion > 20% dropouts - total number of dropouts	8	3159	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.08]
15.1 < 20% dropouts	3	1039	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.14]
15.2 > 20% dropouts	5	2120	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.24]
16 Adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.1 Constipation	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.2 Diarrhoea	7		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.3 Dry mouth	8		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.4 Nausea	8		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.5 Vomiting	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.6 Abdominal pain upper	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.7 Dyspepsia	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.8 Abdominal discomfort	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.9 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.10 Stomach discomfort	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.11 Flatulence	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.12 Fatigue	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.13 Irritability	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.14 Decreased appetite	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.15 Anorexia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.16 Dizziness	8		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.17 Headache	8		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.18 Somnolence	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.19 Tremor	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.20 Sedation	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.21 Dysgeusia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.22 Poor quality sleep	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.23 Ejaculation delayed (men)	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.24 Erectile dysfunction (men)	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.25 Hyperhidrosis	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.26 Vision blurred	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.27 Nasopharyngitis	4		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.28 Upper respiratory tract infection	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.29 Gastroenteritis viral	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.30 Urinary tract infection bacterial	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.31 Anorgasmia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.32 Insomnia	5		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.33 Restlessness	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.34 Abnormal dreams	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.35 Anxiety	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.36 Depression	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.37 Libido decreased	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

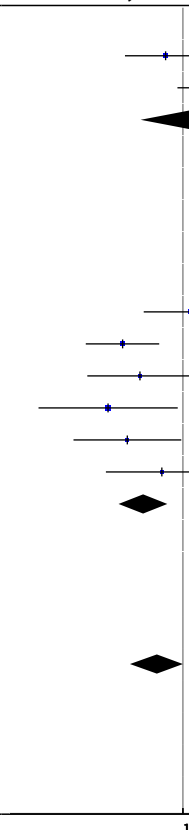
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.38 Orgasm abnormal	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.39 Nightmare	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.40 Middle insomnia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.41 Palpitations	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.42 Tinnitus	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.43 Back pain	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.44 Arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.45 Myalgia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.46 Musculoskeletal pain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.47 Muscle spasms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.48 Pain in extremity	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.49 Hot flush	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.50 Fall	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.51 Muscle strain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.52 Accidental overdose	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.53 Yawning	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.54 Rhinorrhoea	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.55 Weight decreased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.56 Blood pressure increased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16.57 Heart rate increased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Serious adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17.1 Varicella zoster infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.2 Brain tumour	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 Gallbladder cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.4 Bile duct cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.5 Prostate cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.6 Worsening of major depressive disorder	6		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.7 Suicidal ideation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.8 Suicide attempt	3		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.9 Intentional self-injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.10 Self-injurious behaviour	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.11 Panic attack	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.12 Anxiety	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.13 Middle ear effusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.14 Vertigo positional	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.15 Jaundice cholestatic	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.16 Pelvic fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.17 Intentional overdose	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.18 Lumbar vertebral fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.19 Hip fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.20 Head injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.21 Stress fracture	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.22 Craniocerebral injury	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.23 Subdural haematoma	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.24 Asthenia	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.25 Serotonin syndrome	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.26 Dizziness	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.27 Convulsion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.28 Transient ischaemic attack	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.29 Adenomyosis	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.30 Vaginal haemorrhage	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.31 Varicocele	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.32 Pulmonary embolism	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.33 Blood pressure decreased	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.34 Acute myocardial infarction	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.35 Atrial fibrillation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.36 Coronary artery disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.37 Abortion induced	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17.38 Ligament sprain	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 1 Response.

Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Vortioxetine vs venlafaxine					
Alvarez 2012	140/210	81/114		14.28%	0.94[0.81,1.09]
Wang 2015	139/213	132/230		14.46%	1.14[0.98,1.32]
Subtotal (95% CI)	**423**	**344**		**28.73%**	**1.03[0.85,1.25]**
Total events: 279 (Vortioxetine), 213 (SNRI)					
Heterogeneity: Tau^2=0.01; Chi^2=3.21, df=1(P=0.07); I^2=68.83%					
Test for overall effect: Z=0.34(P=0.73)					
2.1.2 Vortioxetine vs duloxetine					
Baldwin 2012	174/312	85/157		12.88%	1.03[0.87,1.23]
Boulenger 2014	178/303	108/147		15.26%	0.8[0.7,0.92]
Katona 2012	82/156	93/151		11.73%	0.85[0.7,1.04]
Mahableshwarkar 2013	58/153	76/152		8.81%	0.76[0.59,0.98]
Mahableshwarkar 2015a	129/301	80/152		11.51%	0.81[0.67,0.99]
Mahableshwarkar 2015b	89/198	102/210		11.08%	0.93[0.75,1.14]
Subtotal (95% CI)	**1423**	**969**		**71.27%**	**0.86[0.79,0.94]**
Total events: 710 (Vortioxetine), 544 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=6.93, df=5(P=0.23); I^2=27.83%					
Test for overall effect: Z=3.21(P=0)					
Total (95% CI)	**1846**	**1313**		**100%**	**0.91[0.82,1]**
Total events: 989 (Vortioxetine), 757 (SNRI)					
Heterogeneity: Tau^2=0.01; Chi^2=17.79, df=7(P=0.01); I^2=60.64%					
Test for overall effect: Z=1.88(P=0.06)					
Test for subgroup differences: Chi^2=2.84, df=1 (P=0.09), I^2=64.84%					



Analysis 2.2. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 2 Total number of dropouts.

Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Vortioxetine vs venlafaxine					
Alvarez 2012	30/210	21/114		9.92%	0.78[0.47,1.29]
Wang 2015	38/213	62/230		14.88%	0.66[0.46,0.95]
Subtotal (95% CI)	**423**	**344**		**24.8%**	**0.7[0.52,0.93]**
Total events: 68 (Vortioxetine), 83 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=2.41(P=0.02)					
2.2.2 Vortioxetine vs duloxetine					
Baldwin 2012	73/312	44/157		16.46%	0.83[0.61,1.15]
Boulenger 2014	61/303	16/147		9.79%	1.85[1.11,3.09]
Katona 2012	20/156	23/151		8.8%	0.84[0.48,1.47]
Mahableshwarkar 2013	31/153	42/152		13.05%	0.73[0.49,1.1]
Mahableshwarkar 2015a	75/301	37/152		15.55%	1.02[0.73,1.44]
Mahableshwarkar 2015b	30/198	34/210		11.56%	0.94[0.6,1.47]
Subtotal (95% CI)	**1423**	**969**		**75.2%**	**0.96[0.76,1.21]**
Total events: 290 (Vortioxetine), 196 (SNRI)					
Heterogeneity: Tau^2=0.04; Chi^2=9.07, df=5(P=0.11); I^2=44.9%					
Test for overall effect: Z=0.33(P=0.74)					
Total (95% CI)	**1846**	**1313**		**100%**	**0.89[0.73,1.08]**
Total events: 358 (Vortioxetine), 279 (SNRI)					
Heterogeneity: Tau^2=0.03; Chi^2=12.46, df=7(P=0.09); I^2=43.83%					
Test for overall effect: Z=1.15(P=0.25)					
Test for subgroup differences: Chi^2=2.87, df=1 (P=0.09), I^2=65.17%					

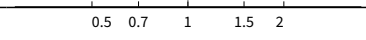
Favours vortioxetine | Favours SNRI

Analysis 2.3. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 3 Remission.

Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Vortioxetine vs venlafaxine					
Alvarez 2012	102/210	62/114		15.18%	0.89[0.72,1.11]
Wang 2015	90/213	89/230		14.82%	1.09[0.87,1.37]
Subtotal (95% CI)	**423**	**344**		**30%**	**0.99[0.81,1.2]**
Total events: 192 (Vortioxetine), 151 (SNRI)					
Heterogeneity: Tau^2=0.01; Chi^2=1.59, df=1(P=0.21); I^2=37.25%					
Test for overall effect: Z=0.15(P=0.88)					
2.3.2 Vortioxetine vs duloxetine					
Baldwin 2012	110/312	52/157		12.97%	1.06[0.81,1.39]
Boulenger 2014	110/300	79/146		15.53%	0.68[0.55,0.84]
Katona 2012	45/156	51/151		10.54%	0.85[0.61,1.19]
Mahableshwarkar 2013	32/153	51/152		9.03%	0.62[0.43,0.91]

Favours SNRI | Favours vortioxetine

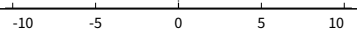
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2015a	82/301	38/152		10.57%	1.09[0.78,1.52]
Mahableshwarkar 2015b	53/198	63/210		11.36%	0.89[0.65,1.22]
Subtotal (95% CI)	**1420**	**968**		**70%**	**0.85[0.7,1.02]**
Total events: 432 (Vortioxetine), 334 (SNRI)					
Heterogeneity: Tau^2=0.03; Chi^2=11.94, df=5(P=0.04); I^2=58.11%					
Test for overall effect: Z=1.71(P=0.09)					
Total (95% CI)	**1843**	**1312**		**100%**	**0.89[0.77,1.03]**
Total events: 624 (Vortioxetine), 485 (SNRI)					
Heterogeneity: Tau^2=0.02; Chi^2=16.15, df=7(P=0.02); I^2=56.66%					
Test for overall effect: Z=1.59(P=0.11)					
Test for subgroup differences: Chi^2=1.15, df=1 (P=0.28), I^2=13.14%					



Favours SNRI — Favours vortioxetine

Analysis 2.4. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 4 Depressive symptoms.

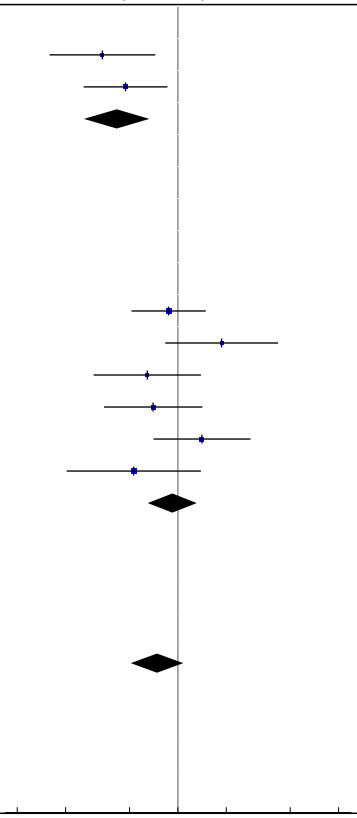
Study or subgroup	Vortioxetine N	Vortioxetine Mean(SD)	SNRI N	SNRI Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.4.1 Vortioxetine vs venlafaxine							
Alvarez 2012	182	-22 (9.5)	95	-23.4 (8.8)		11.3%	1.37[-0.87,3.61]
Wang 2015	209	-19.4 (10.1)	215	-18.2 (10.3)		13.06%	-1.2[-3.14,0.74]
Subtotal ***	**391**		**310**			**24.36%**	**0.02[-2.49,2.54]**
Heterogeneity: Tau^2=2.16; Chi^2=2.9, df=1(P=0.09); I^2=65.47%							
Test for overall effect: Z=0.02(P=0.99)							
2.4.2 Vortioxetine vs duloxetine							
Baldwin 2012	241	-18.4 (8.8)	112	-18.9 (8.5)		13.19%	0.5[-1.42,2.42]
Boulenger 2014	300	-18 (9.6)	146	-21.2 (9.3)		13.58%	3.18[1.32,5.04]
Katona 2012	155	-15.5 (9.3)	148	-18 (9.3)		12.11%	2.5[0.41,4.59]
Mahableshwarkar 2013	153	-11.3 (9.9)	149	-14.1 (9.9)		11.34%	2.8[0.57,5.03]
Mahableshwarkar 2015a	225	-14.9 (9.4)	115	-16.9 (9.5)		11.94%	2[-0.12,4.12]
Mahableshwarkar 2015b	175	-14.3 (9)	187	-15.5 (9.2)		13.48%	1.2[-0.68,3.08]
Subtotal ***	**1249**		**857**			**75.64%**	**1.99[1.15,2.83]**
Heterogeneity: Tau^2=0.06; Chi^2=5.3, df=5(P=0.38); I^2=5.72%							
Test for overall effect: Z=4.63(P<0.0001)							
Total ***	**1640**		**1167**			**100%**	**1.52[0.5,2.53]**
Heterogeneity: Tau^2=1.08; Chi^2=14.12, df=7(P=0.05); I^2=50.43%							
Test for overall effect: Z=2.92(P=0)							
Test for subgroup differences: Chi^2=2.11, df=1 (P=0.15), I^2=52.65%							



Favours vortioxetine — Favours SNRI

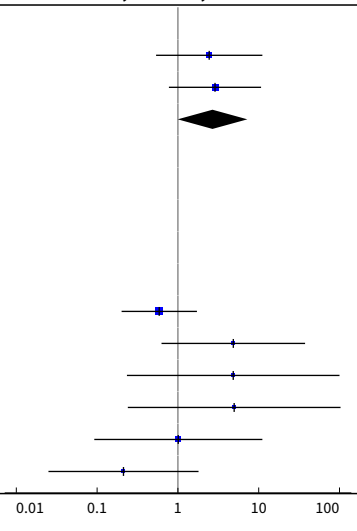
Analysis 2.5. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 5 Dropout due to adverse events.

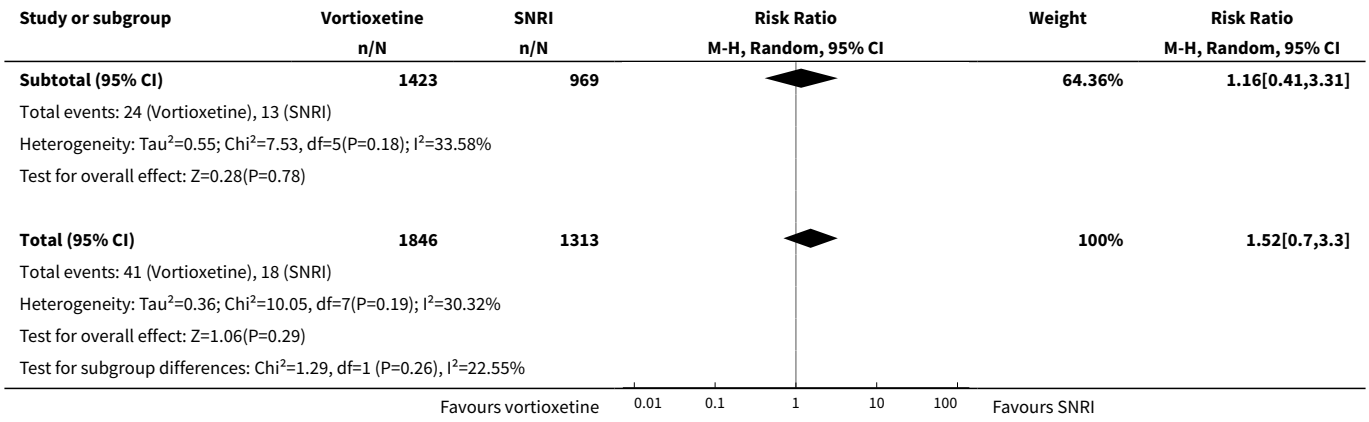
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Vortioxetine vs venlafaxine					
Alvarez 2012	10/210	16/114		11.92%	0.34[0.16,0.72]
Wang 2015	14/213	32/230		14.53%	0.47[0.26,0.86]
Subtotal (95% CI)	**423**	**344**		**26.46%**	**0.42[0.26,0.67]**
Total events: 24 (Vortioxetine), 48 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=0.45, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=3.66(P=0)					
2.5.2 Vortioxetine vs duloxetine					
Baldwin 2012	33/312	19/157		15.8%	0.87[0.51,1.49]
Boulenger 2014	27/303	7/147		11.17%	1.87[0.83,4.2]
Katona 2012	10/156	15/151		11.74%	0.65[0.3,1.39]
Mahableshwarkar 2013	12/153	17/152		12.75%	0.7[0.35,1.42]
Mahableshwarkar 2015a	28/301	10/152		12.89%	1.41[0.71,2.83]
Mahableshwarkar 2015b	6/198	12/210		9.19%	0.53[0.2,1.39]
Subtotal (95% CI)	**1423**	**969**		**73.54%**	**0.92[0.65,1.31]**
Total events: 116 (Vortioxetine), 80 (SNRI)					
Heterogeneity: Tau^2=0.06; Chi^2=7.14, df=5(P=0.21); I^2=29.98%					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**1846**	**1313**		**100%**	**0.74[0.51,1.08]**
Total events: 140 (Vortioxetine), 128 (SNRI)					
Heterogeneity: Tau^2=0.16; Chi^2=15.63, df=7(P=0.03); I^2=55.22%					
Test for overall effect: Z=1.56(P=0.12)					
Test for subgroup differences: Chi^2=7.07, df=1 (P=0.01), I^2=85.86%					



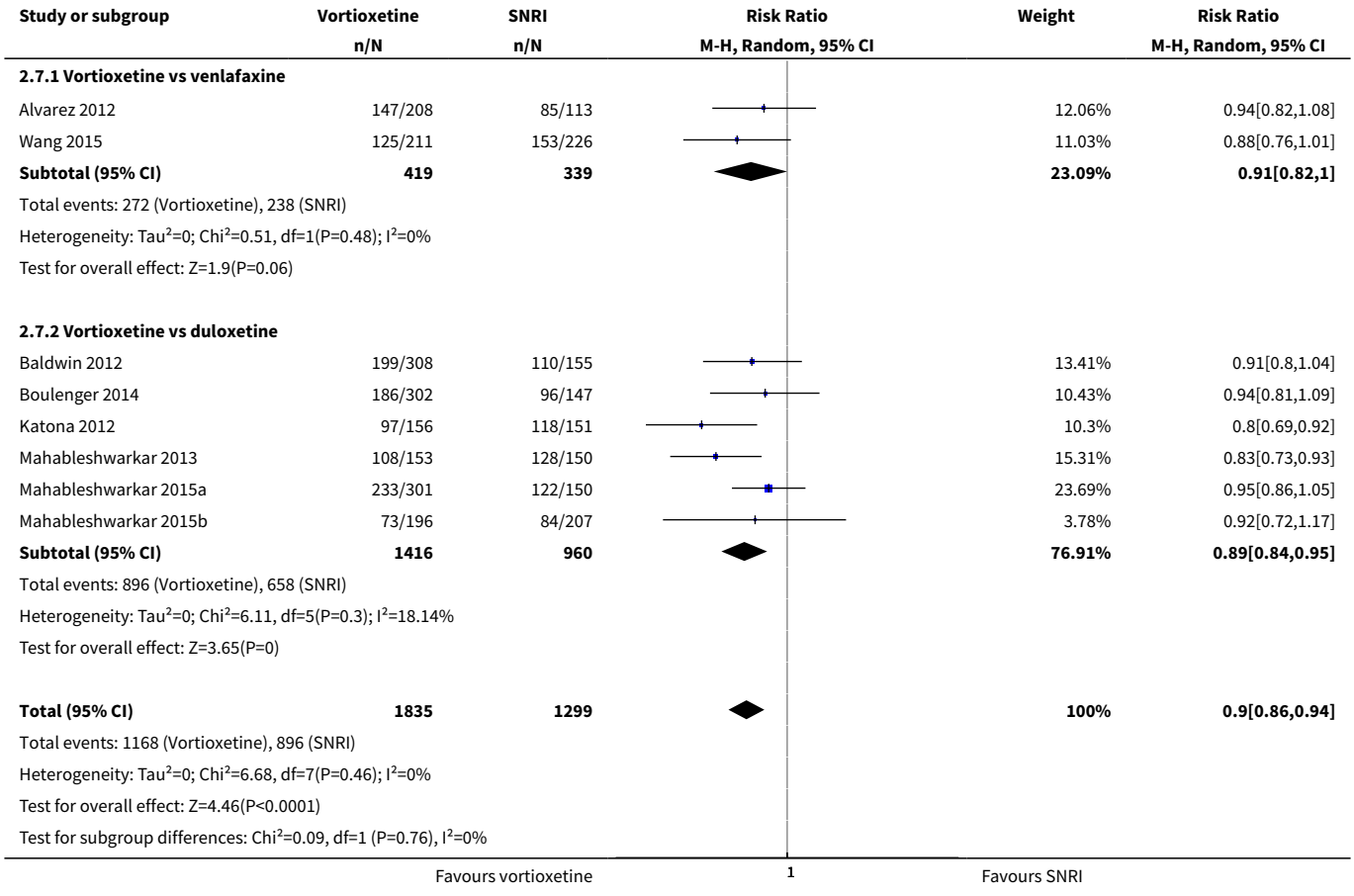
Analysis 2.6. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 6 Dropout due to inefficacy.

Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Vortioxetine vs venlafaxine					
Alvarez 2012	9/210	2/114		16.32%	2.44[0.54,11.11]
Wang 2015	8/213	3/230		19.31%	2.88[0.77,10.71]
Subtotal (95% CI)	**423**	**344**		**35.64%**	**2.68[0.99,7.24]**
Total events: 17 (Vortioxetine), 5 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					
2.6.2 Vortioxetine vs duloxetine					
Baldwin 2012	7/312	6/157		23.69%	0.59[0.2,1.72]
Boulenger 2014	10/303	1/147		10.78%	4.85[0.63,37.54]
Katona 2012	2/156	0/151		5.69%	4.84[0.23,100.01]
Mahableshwarkar 2013	2/153	0/152		5.69%	4.97[0.24,102.62]
Mahableshwarkar 2015a	2/301	1/152		8.44%	1.01[0.09,11.05]
Mahableshwarkar 2015b	1/198	5/210		10.08%	0.21[0.03,1.8]



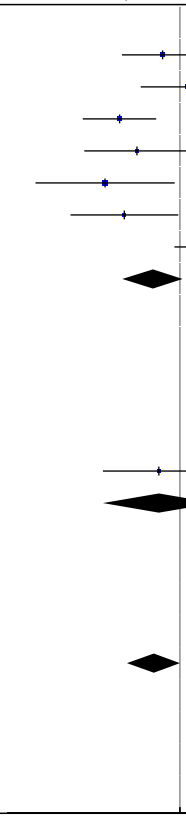


Analysis 2.7. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 7 Tolerability.



Analysis 2.8. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 8 Subgroup analysis: fixed vs flexible dosing - response.

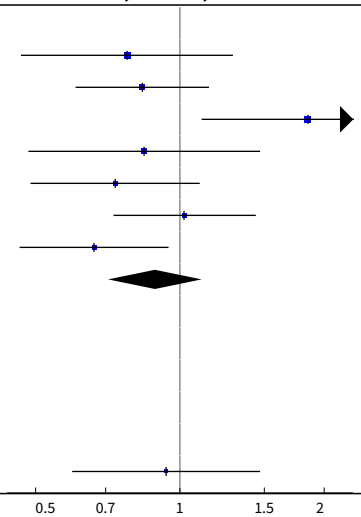
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Fixed dosing					
Alvarez 2012	140/210	81/114		14.28%	0.94[0.81,1.09]
Baldwin 2012	174/312	85/157		12.88%	1.03[0.87,1.23]
Boulenger 2014	178/303	108/147		15.26%	0.8[0.7,0.92]
Katona 2012	82/156	93/151		11.73%	0.85[0.7,1.04]
Mahableshwarkar 2013	58/153	76/152		8.81%	0.76[0.59,0.98]
Mahableshwarkar 2015a	129/301	80/152		11.51%	0.81[0.67,0.99]
Wang 2015	139/213	132/230		14.46%	1.14[0.98,1.32]
Subtotal (95% CI)	**1648**	**1103**		**88.92%**	**0.91[0.81,1.01]**
Total events: 900 (Experimental), 655 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=17.78, df=6(P=0.01); I^2=66.25%					
Test for overall effect: Z=1.72(P=0.09)					
2.8.2 Flexible dosing					
Mahableshwarkar 2015b	89/198	102/210		11.08%	0.93[0.75,1.14]
Subtotal (95% CI)	**198**	**210**		**11.08%**	**0.93[0.75,1.14]**
Total events: 89 (Experimental), 102 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.46)					
Total (95% CI)	**1846**	**1313**		**100%**	**0.91[0.82,1]**
Total events: 989 (Experimental), 757 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=17.79, df=7(P=0.01); I^2=60.64%					
Test for overall effect: Z=1.88(P=0.06)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.86), I^2=0%					



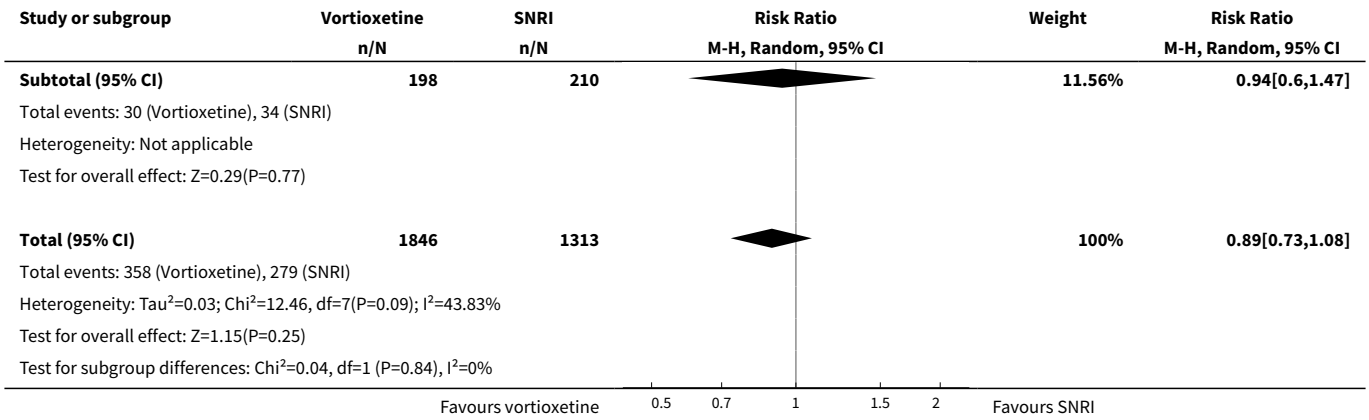
Favours SNRI — Favours vortioxetine

Analysis 2.9. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 9 Subgroup analysis: fixed vs flexible dosing - total number of dropouts.

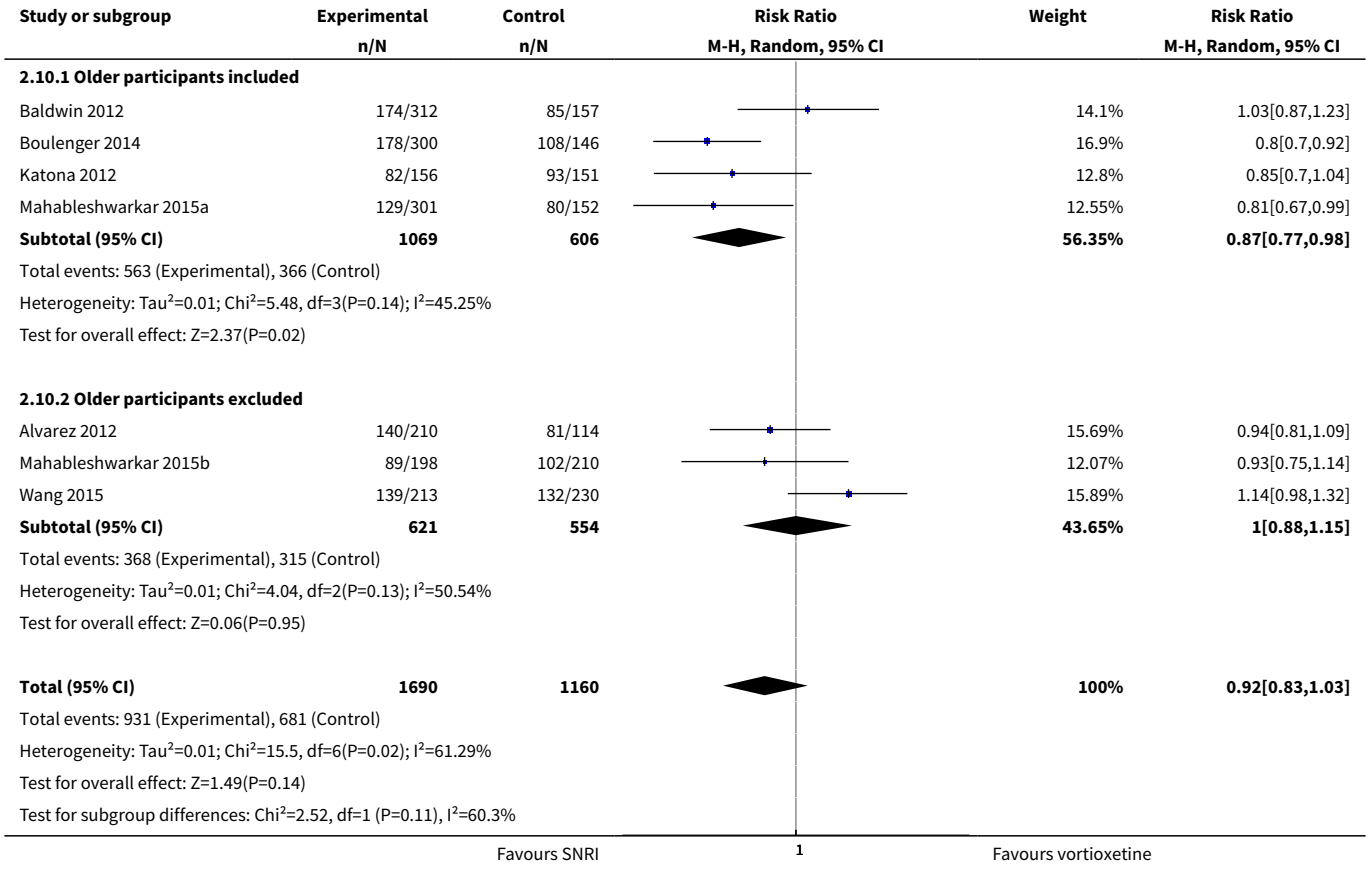
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.9.1 Fixed dosing					
Alvarez 2012	30/210	21/114		9.92%	0.78[0.47,1.29]
Baldwin 2012	73/312	44/157		16.46%	0.83[0.61,1.15]
Boulenger 2014	61/303	16/147		9.79%	1.85[1.11,3.09]
Katona 2012	20/156	23/151		8.8%	0.84[0.48,1.47]
Mahableshwarkar 2013	31/153	42/152		13.05%	0.73[0.49,1.1]
Mahableshwarkar 2015a	75/301	37/152		15.55%	1.02[0.73,1.44]
Wang 2015	38/213	62/230		14.88%	0.66[0.46,0.95]
Subtotal (95% CI)	**1648**	**1103**		**88.44%**	**0.89[0.71,1.11]**
Total events: 328 (Vortioxetine), 245 (SNRI)					
Heterogeneity: Tau^2=0.05; Chi^2=12.38, df=6(P=0.05); I^2=51.55%					
Test for overall effect: Z=1.04(P=0.3)					
2.9.2 Flexible dosing					
Mahableshwarkar 2015b	30/198	34/210		11.56%	0.94[0.6,1.47]



Favours vortioxetine — Favours SNRI

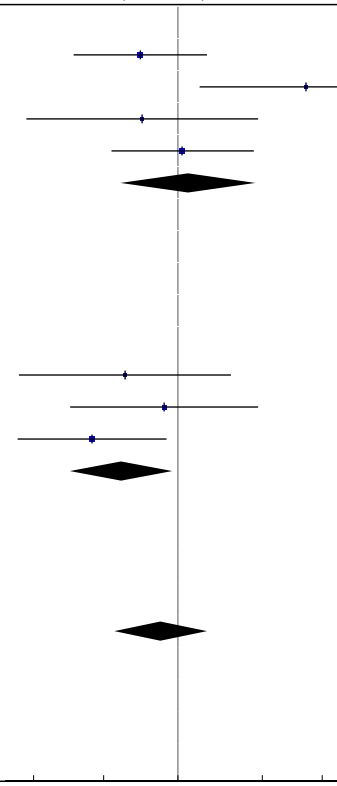


Analysis 2.10. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 10 Subgroup analysis: inclusion of older (aged > 65 years) participants - response.



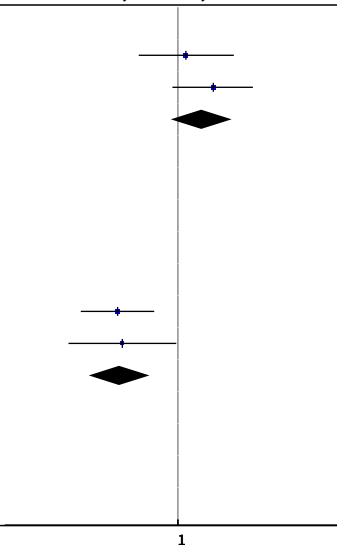
Analysis 2.11. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 11 Subgroup analysis: inclusion of older (aged > 65 years) participants - total number of dropouts.

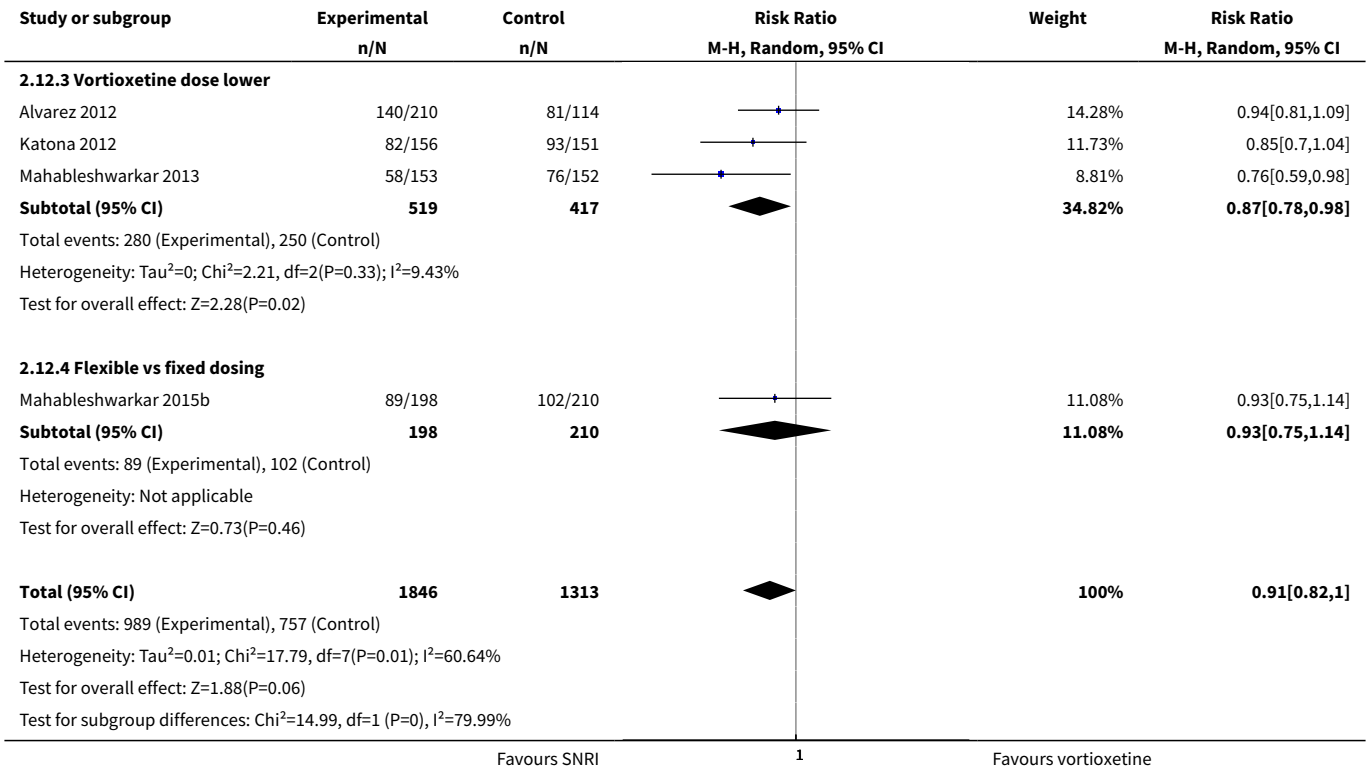
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Older participants included					
Baldwin 2012	73/312	44/157		18.53%	0.83[0.61,1.15]
Boulenger 2014	61/303	16/147		11.5%	1.85[1.11,3.09]
Katona 2012	20/156	23/151		10.4%	0.84[0.48,1.47]
Mahableshwarkar 2015a	75/301	37/152		17.6%	1.02[0.73,1.44]
Subtotal (95% CI)	**1072**	**607**		**58.02%**	**1.05[0.76,1.45]**
Total events: 229 (Vortioxetine), 120 (SNRI)					
Heterogeneity: Tau^2=0.06; Chi^2=7.18, df=3(P=0.07); I^2=58.22%					
Test for overall effect: Z=0.28(P=0.78)					
2.11.2 Older participants excluded					
Alvarez 2012	30/210	21/114		11.64%	0.78[0.47,1.29]
Mahableshwarkar 2015b	30/198	34/210		13.42%	0.94[0.6,1.47]
Wang 2015	38/213	62/230		16.91%	0.66[0.46,0.95]
Subtotal (95% CI)	**621**	**554**		**41.98%**	**0.76[0.6,0.97]**
Total events: 98 (Vortioxetine), 117 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=1.4, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=2.18(P=0.03)					
Total (95% CI)	**1693**	**1161**		**100%**	**0.92[0.74,1.15]**
Total events: 327 (Vortioxetine), 237 (SNRI)					
Heterogeneity: Tau^2=0.04; Chi^2=11.59, df=6(P=0.07); I^2=48.22%					
Test for overall effect: Z=0.75(P=0.45)					
Test for subgroup differences: Chi^2=2.38, df=1 (P=0.12), I^2=58.06%					



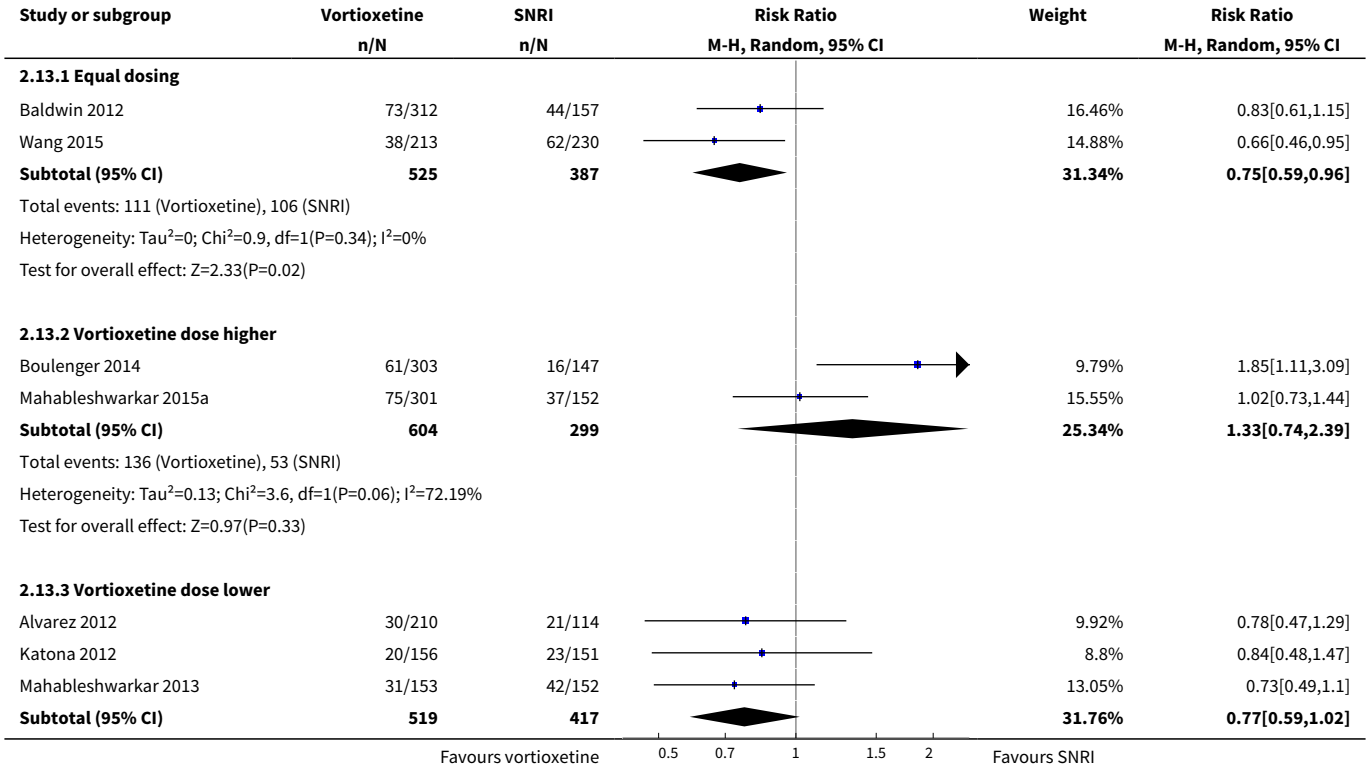
Analysis 2.12. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 12 Sensitivity analysis - unequal dosing - response.

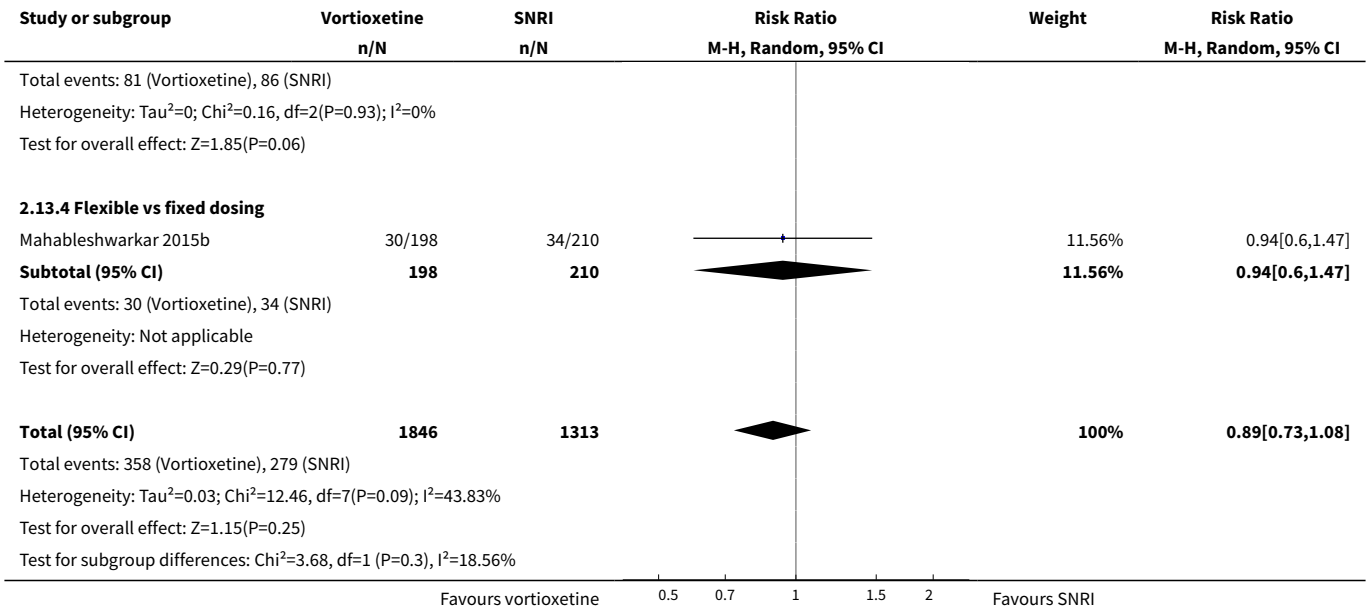
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 Equal dosing					
Baldwin 2012	174/312	85/157		12.88%	1.03[0.87,1.23]
Wang 2015	139/213	132/230		14.46%	1.14[0.98,1.32]
Subtotal (95% CI)	**525**	**387**		**27.33%**	**1.09[0.97,1.22]**
Total events: 313 (Experimental), 217 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.72, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=1.51(P=0.13)					
2.12.2 Vortioxetine dose higher					
Boulenger 2014	178/303	108/147		15.26%	0.8[0.7,0.92]
Mahableshwarkar 2015a	129/301	80/152		11.51%	0.81[0.67,0.99]
Subtotal (95% CI)	**604**	**299**		**26.77%**	**0.8[0.72,0.9]**
Total events: 307 (Experimental), 188 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=3.81(P=0)					



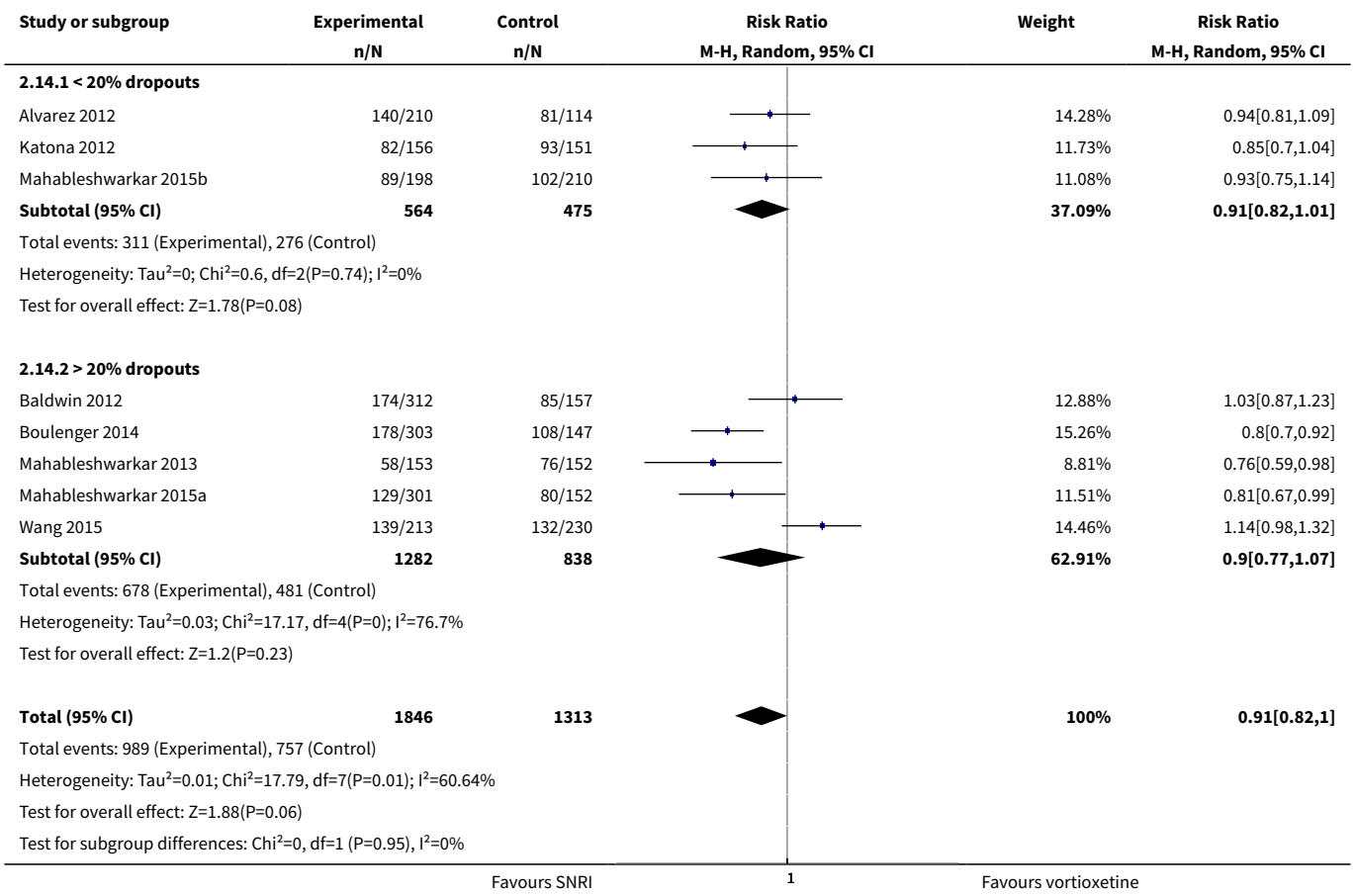


Analysis 2.13. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 13 Sensitivity analysis - unequal dosing - total number of dropouts.



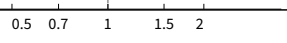


Analysis 2.14. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 14 Sensitivity analysis - exclusion > 20% dropouts - response.



Analysis 2.15. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 15 Sensitivity analysis - exclusion > 20% dropouts - total number of dropouts.

Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.15.1 < 20% dropouts					
Alvarez 2012	30/210	21/114		9.92%	0.78[0.47,1.29]
Katona 2012	20/156	23/151		8.8%	0.84[0.48,1.47]
Mahableshwarkar 2015b	30/198	34/210		11.56%	0.94[0.6,1.47]
Subtotal (95% CI)	**564**	**475**		**30.28%**	**0.86[0.64,1.14]**
Total events: 80 (Vortioxetine), 78 (SNRI)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=1.05(P=0.29)					
2.15.2 > 20% dropouts					
Baldwin 2012	73/312	44/157		16.46%	0.83[0.61,1.15]
Boulenger 2014	61/303	16/147		9.79%	1.85[1.11,3.09]
Mahableshwarkar 2013	31/153	42/152		13.05%	0.73[0.49,1.1]
Mahableshwarkar 2015a	75/301	37/152		15.55%	1.02[0.73,1.44]
Wang 2015	38/213	62/230		14.88%	0.66[0.46,0.95]
Subtotal (95% CI)	**1282**	**838**		**69.72%**	**0.92[0.68,1.24]**
Total events: 278 (Vortioxetine), 201 (SNRI)					
Heterogeneity: Tau^2=0.08; Chi^2=12.14, df=4(P=0.02); I^2=67.05%					
Test for overall effect: Z=0.56(P=0.58)					
Total (95% CI)	**1846**	**1313**		**100%**	**0.89[0.73,1.08]**
Total events: 358 (Vortioxetine), 279 (SNRI)					
Heterogeneity: Tau^2=0.03; Chi^2=12.46, df=7(P=0.09); I^2=43.83%					
Test for overall effect: Z=1.15(P=0.25)					
Test for subgroup differences: Chi^2=0.11, df=1 (P=0.74), I^2=0%					



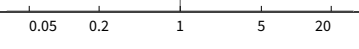
Favours vortioxetine — Favours SNRI

Analysis 2.16. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 16 Adverse events.

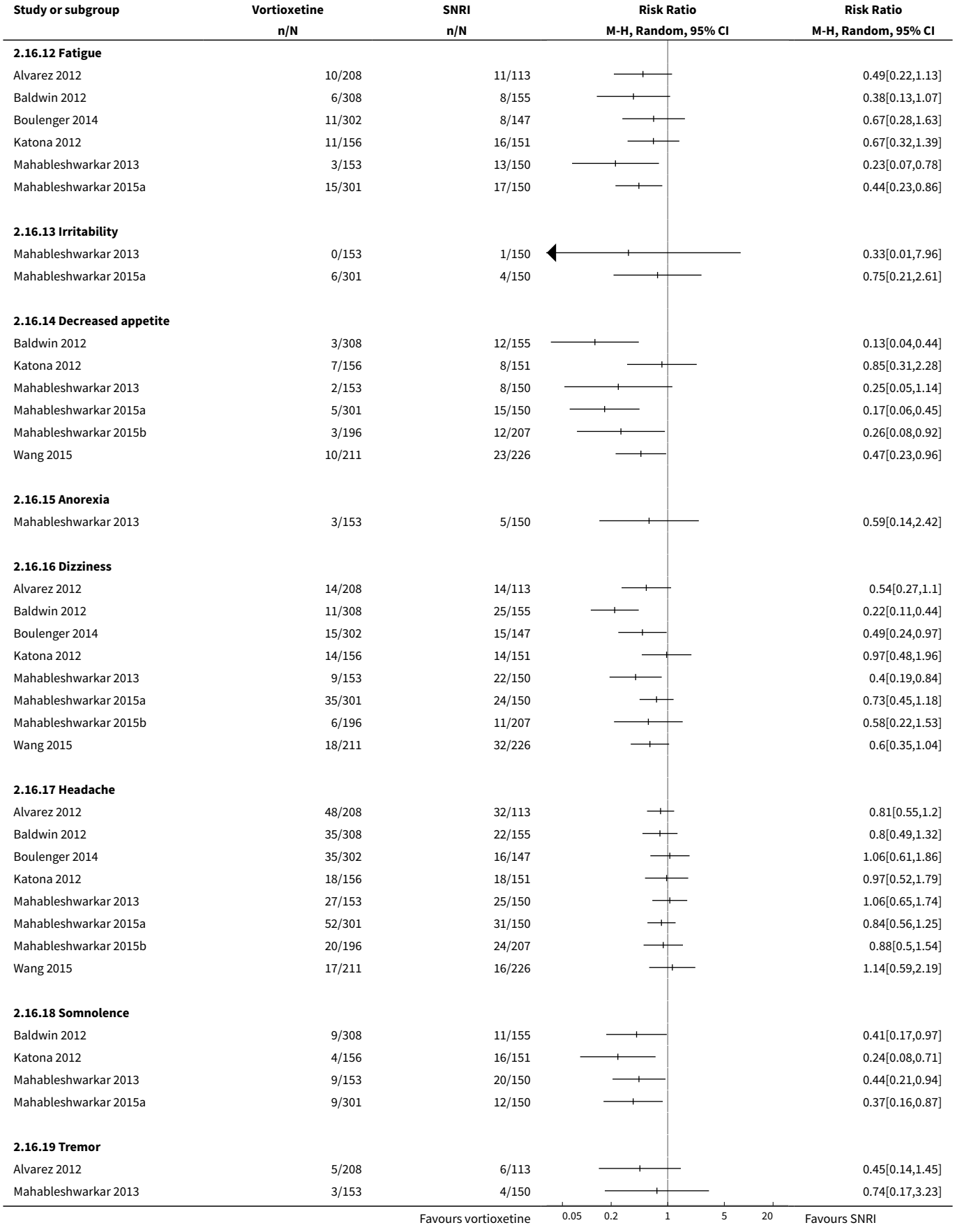
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.16.1 Constipation				
Alvarez 2012	4/208	11/113		0.2[0.06,0.61]
Baldwin 2012	8/308	10/155		0.4[0.16,1]
Katona 2012	10/156	21/151		0.46[0.22,0.95]
Mahableshwarkar 2013	6/153	18/150		0.33[0.13,0.8]
Mahableshwarkar 2015a	22/301	18/150		0.61[0.34,1.1]
Wang 2015	9/211	18/226		0.54[0.25,1.17]
2.16.2 Diarrhoea				
Alvarez 2012	16/208	5/113		1.74[0.65,4.62]
Baldwin 2012	11/308	7/155		0.79[0.31,2]
Boulenger 2014	17/302	9/147		0.92[0.42,2.01]
Katona 2012	8/156	14/151		0.55[0.24,1.28]

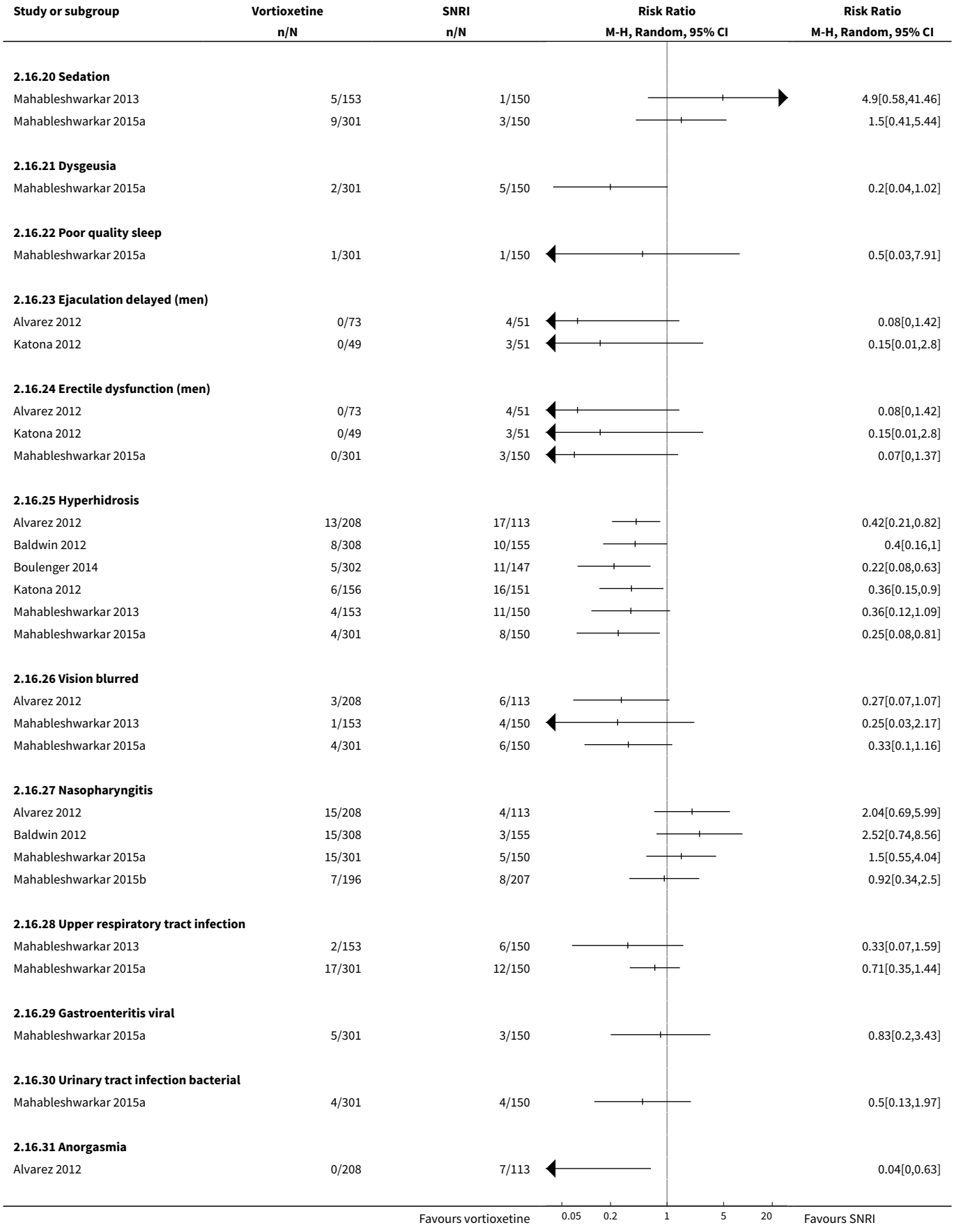
Favours vortioxetine — Favours SNRI

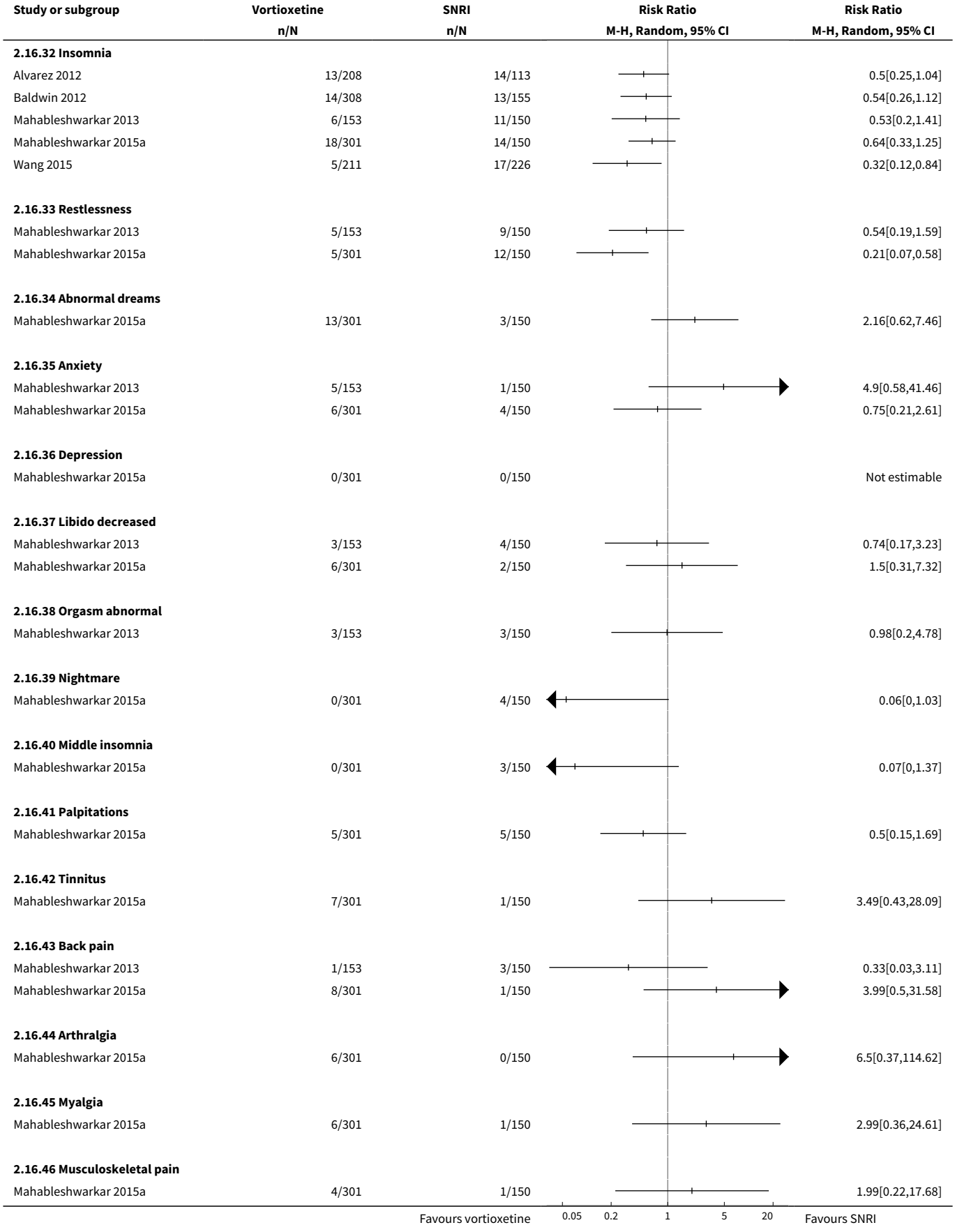
Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mahableshwarkar 2013	14/153	19/150		0.72[0.38,1.39]
Mahableshwarkar 2015a	34/301	19/150		0.89[0.53,1.51]
Mahableshwarkar 2015b	11/196	6/207		1.94[0.73,5.14]
2.16.3 Dry mouth				
Alvarez 2012	16/208	19/113		0.46[0.25,0.85]
Baldwin 2012	15/308	12/155		0.63[0.3,1.31]
Boulenger 2014	14/302	14/147		0.49[0.24,0.99]
Katona 2012	10/156	33/151		0.29[0.15,0.57]
Mahableshwarkar 2013	16/153	40/150		0.39[0.23,0.67]
Mahableshwarkar 2015a	36/301	26/150		0.69[0.43,1.1]
Mahableshwarkar 2015b	6/196	16/207		0.4[0.16,0.99]
Wang 2015	12/211	24/226		0.54[0.27,1.04]
2.16.4 Nausea				
Alvarez 2012	70/208	38/113		1[0.73,1.38]
Baldwin 2012	59/308	52/155		0.57[0.42,0.79]
Boulenger 2014	88/302	45/147		0.95[0.7,1.29]
Katona 2012	34/156	50/151		0.66[0.45,0.96]
Mahableshwarkar 2013	44/153	63/150		0.68[0.5,0.94]
Mahableshwarkar 2015a	103/301	55/150		0.93[0.72,1.21]
Mahableshwarkar 2015b	40/196	43/207		0.98[0.67,1.44]
Wang 2015	51/211	53/226		1.03[0.74,1.44]
2.16.5 Vomiting				
Alvarez 2012	11/208	4/113		1.49[0.49,4.58]
Baldwin 2012	13/308	11/155		0.59[0.27,1.3]
Mahableshwarkar 2013	7/153	5/150		1.37[0.45,4.23]
Mahableshwarkar 2015a	20/301	12/150		0.83[0.42,1.65]
2.16.6 Abdominal pain upper				
Mahableshwarkar 2013	6/153	2/150		2.94[0.6,14.34]
Mahableshwarkar 2015a	9/301	4/150		1.12[0.35,3.58]
2.16.7 Dyspepsia				
Mahableshwarkar 2013	3/153	2/150		1.47[0.25,8.68]
Mahableshwarkar 2015a	11/301	7/150		0.78[0.31,1.98]
Wang 2015	11/211	9/226		1.31[0.55,3.1]
2.16.8 Abdominal discomfort				
Mahableshwarkar 2015a	8/301	1/150		3.99[0.5,31.58]
2.16.9 Abdominal pain				
Mahableshwarkar 2013	0/153	5/150		0.09[0,1.6]
2.16.10 Stomach discomfort				
Mahableshwarkar 2013	4/153	1/150		3.92[0.44,34.68]
2.16.11 Flatulence				
Mahableshwarkar 2013	3/153	1/150		2.94[0.31,27.96]
Mahableshwarkar 2015a	6/301	2/150		1.5[0.31,7.32]

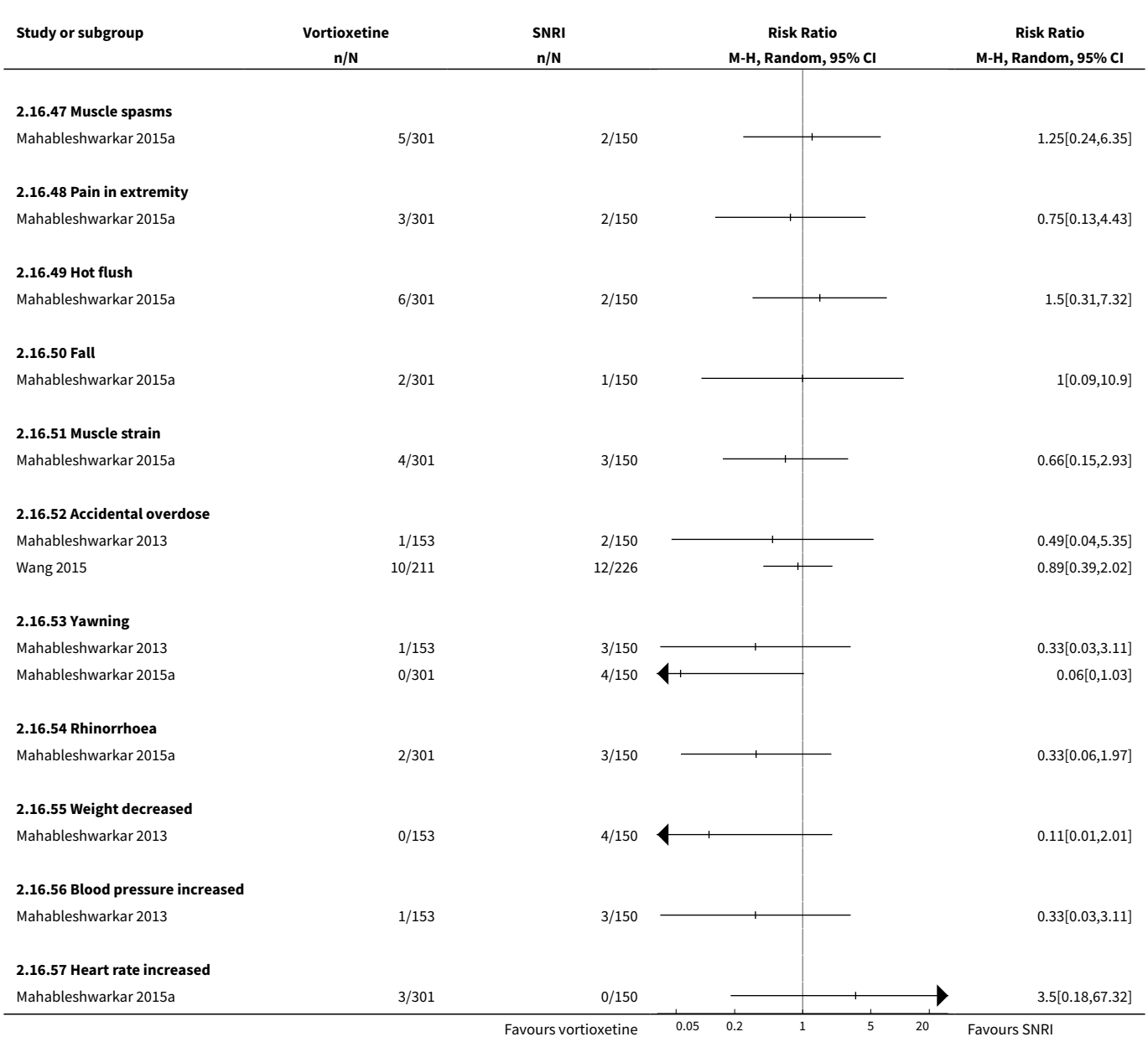


Favours vortioxetine Favours SNRI

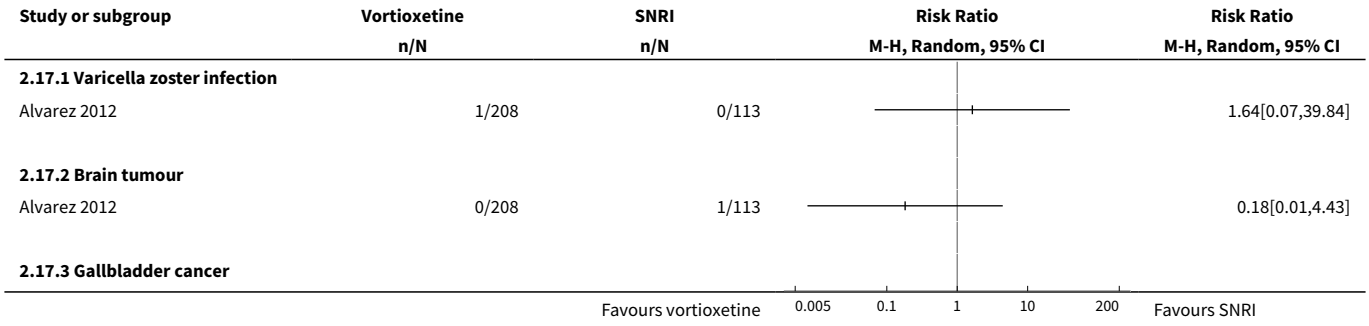




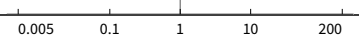




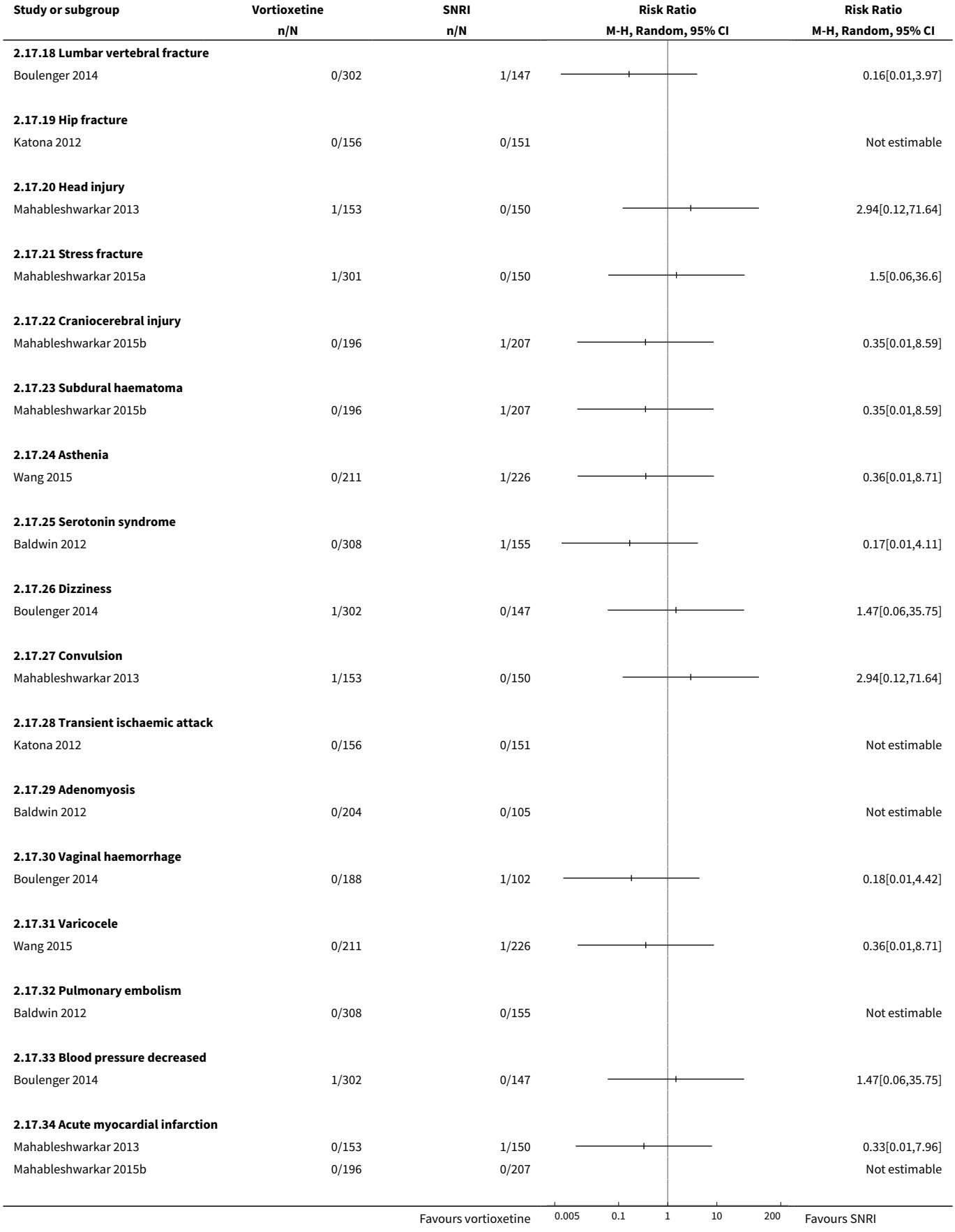
Analysis 2.17. Comparison 2 Vortioxetine versus serotonin-norepinephrine reuptake inhibitors (SNRIs), Outcome 17 Serious adverse events.

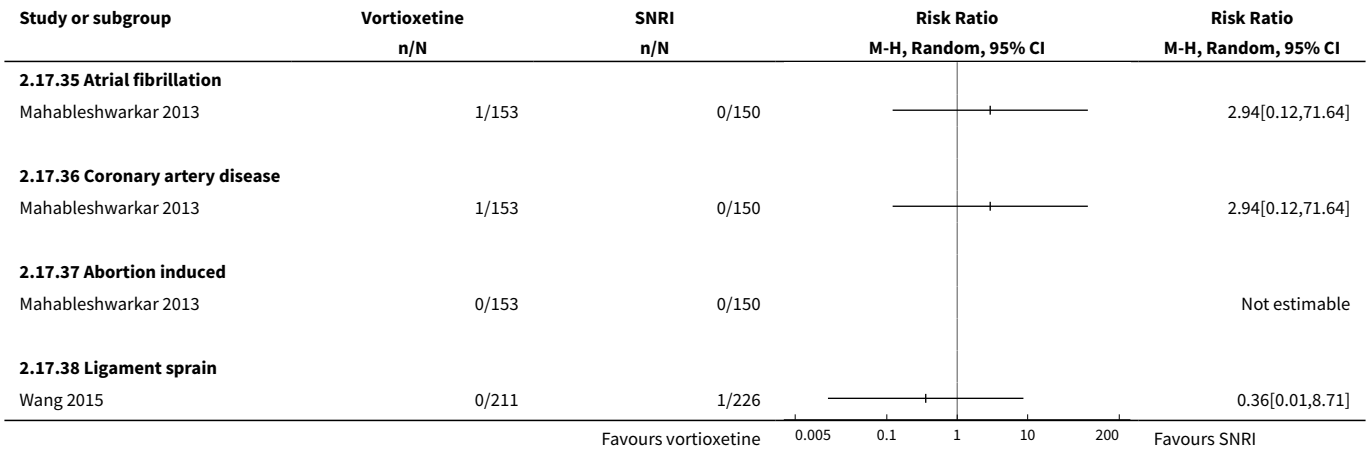


Study or subgroup	Vortioxetine n/N	SNRI n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Baldwin 2012	1/308	0/155		1.51[0.06,36.96]
2.17.4 Bile duct cancer				
Katona 2012	0/156	0/151		Not estimable
2.17.5 Prostate cancer				
Katona 2012	0/49	1/51		0.35[0.01,8.31]
2.17.6 Worsening of major depressive disorder				
Alvarez 2012	1/208	0/113		1.64[0.07,39.84]
Baldwin 2012	2/308	0/155		2.52[0.12,52.26]
Katona 2012	1/156	0/151		2.9[0.12,70.74]
Mahableshwarkar 2013	0/153	0/150		Not estimable
Mahableshwarkar 2015b	0/196	0/207		Not estimable
Wang 2015	1/211	1/226		1.07[0.07,17.02]
2.17.7 Suicidal ideation				
Mahableshwarkar 2015a	1/301	0/150		1.5[0.06,36.6]
2.17.8 Suicide attempt				
Baldwin 2012	1/308	0/155		1.51[0.06,36.96]
Mahableshwarkar 2015b	1/196	0/207		3.17[0.13,77.29]
Wang 2015	1/211	2/226		0.54[0.05,5.86]
2.17.9 Intentional self-injury				
Boulenger 2014	1/302	0/147		1.47[0.06,35.75]
2.17.10 Self-injurious behaviour				
Boulenger 2014	0/302	1/147		0.16[0.01,3.97]
2.17.11 Panic attack				
Mahableshwarkar 2013	0/153	1/150		0.33[0.01,7.96]
2.17.12 Anxiety				
Wang 2015	0/211	1/226		0.36[0.01,8.71]
2.17.13 Middle ear effusion				
Baldwin 2012	0/308	1/155		0.17[0.01,4.11]
2.17.14 Vertigo positional				
Wang 2015	0/211	1/226		0.36[0.01,8.71]
2.17.15 Jaundice cholestatic				
Baldwin 2012	1/308	0/155		1.51[0.06,36.96]
2.17.16 Pelvic fracture				
Baldwin 2012	1/308	0/155		1.51[0.06,36.96]
2.17.17 Intentional overdose				
Boulenger 2014	0/302	1/147		0.16[0.01,3.97]
Wang 2015	0/211	1/226		0.36[0.01,8.71]



Favours vortioxetine — Favours SNRI





CONTRIBUTIONS OF AUTHORS

MK formulated the idea.

MK, GO and CB wrote the protocol.

GO and MK selected the studies, extracted the data and assessed the risk of bias.

JB double-checked data entry and analyses.

MK analysed the data and wrote the first draft of the review.

CB resolved disagreements on study inclusion and provided supervision of data extraction and analyses.

GO and GG created the 'Summary of findings' tables and wrote major parts of the 'Quality of the evidence' section.

All authors reviewed the drafts, contributed to the final text and approved the final version of the review.

DECLARATIONS OF INTEREST

MK: none.

GO: none.

GG: none.

JB: none.

CB: none.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Our protocol stated that we would prefer Hamilton Depression Rating Scale (HAM-D) data to Montgomery-Åsberg Depression Scale (MADRS) data. However, all studies used the MADRS to assess depressive symptoms and eight studies did not use the HAM-D scale (Boulenger 2014; Jacobsen 2015; Mahableshwarkar 2015a; Mahableshwarkar 2015b; Mahableshwarkar 2015c; McIntyre 2014; NCT01255787; Wang 2015). Therefore, to decrease heterogeneity across trials and to be able use a mean difference as a summary score instead of a standardised mean difference, we decided to give preference to the MADRS data.

The protocol stated that "We will include cluster-RCTs [randomised controlled trials] if direct effect estimates are provided that account for the clustering or if sufficient information is were available to account for the clustering that allow an approximation in accordance to the method suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 16.3.4, Higgins 2011). The method suggested by Higgins 2011 requires an estimate of the intracluster correlation coefficient (ICC), which can be thought of the 'similarity' of individuals within the same cluster and often has to be obtained from an external source. The idea of the approximation is to correct the sample size of the trial to its 'effective sample size' by taking a 'design effect' into account. We excluded cluster randomisation with insufficient information for an approximation." As no relevant cluster controlled trials were identified, we shortened the 'Method' section accordingly.

The protocol stated that trials with cross-over designs will be included, but no such studies could be identified.

We decided post-hoc to calculate NNTBs for response and remission to facilitate the interpretation of the effects for these outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Depressive Disorder, Major [*drug therapy]; Duloxetine Hydrochloride [therapeutic use]; Patient Dropouts [statistics & numerical data]; Piperazines [*therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction; Serotonin and Noradrenaline Reuptake Inhibitors [therapeutic use]; Sulfides [*therapeutic use]; Venlafaxine Hydrochloride [therapeutic use]; Vortioxetine

MeSH check words

Adult; Humans