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Original article

Relative efficacy and tolerability of vortioxetine versus selected antidepressants by indirect comparisons of similar clinical studies

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Abstract

Introduction:
Vortioxetine is an antidepressant with multimodal activity which has shown efficacy in major depressive disorder (MDD) patients in six of ten short-term, randomized, placebo-controlled trials (completed end 2012).

Methods:
We performed meta-regression analyses to indirectly compare vortioxetine to seven marketed antidepressants with different mechanisms of action. To ensure study comparability, only experimental drug and placebo arms from placebo-controlled registration studies were included in primary analyses. The main outcomes were efficacy (standardized mean difference in change from baseline to 2 months on primary endpoint [MADRS/HAM-D]), and tolerability (withdrawal rate due to adverse events).

Results:
For efficacy, estimates of treatment effect (negative estimates favor vortioxetine) for vortioxetine versus comparators were: agomelatine, −0.16 ($p = 0.11$); desvenlafaxine, 0.03 ($p = 0.80$); duloxetine, 0.09 ($p = 0.42$); escitalopram, −0.05 ($p = 0.70$); sertraline, −0.04 ($p = 0.83$); venlafaxine IR/XR, 0.12 ($p = 0.33$); and vilazodone, −0.25 ($p = 0.11$). For tolerability, all but one combination was numerically in favor of vortioxetine (odds ratio < 1), although not all differences were statistically significant: agomelatine, 1.77 ($p = 0.03$); desvenlafaxine, 0.58 ($p = 0.04$); duloxetine, 0.75 ($p = 0.26$); escitalopram, 0.67 ($p = 0.28$); sertraline, 0.30 ($p = 0.01$); venlafaxine, 0.47 ($p = 0.01$); and vilazodone, 0.64 ($p = 0.18$). Sensitivity analyses did not significantly alter antidepressant effect estimates or relative ranking.

Conclusion:
These meta-regression data show that vortioxetine offers a comparable or favorable combination of efficacy (measured by MADRS/HAM-D) and tolerability (measured by withdrawal rate due to adverse events) versus other antidepressants in registration studies in MDD. Alternative methods like mixed-treatment comparison and inclusion of all randomized studies and active reference arms may provide complementary information to this analysis (more evidence but also more heterogeneity).

Key messages:
Indirect comparisons based on registration studies allow a useful comparison between a recently approved antidepressant and an approved drug. Vortioxetine offers a comparable or favorable combination of efficacy (measured by MADRS/HAM-D assessments) and tolerability (measured by withdrawal rate due to adverse events) versus other antidepressants in registration studies in MDD.

Introduction

Globally, more than 350 million people of all ages suffer from depression. Depression is the leading cause of disability worldwide and is a major contributor to the global burden of disease[1].

Major depressive disorder (MDD) is a complex and highly disabling condition that severely affects patient health and function, both at home and at work[2,3]. The disability burden of mental and neurological disorders is important. Wittchen *et al.* identified that depression has already become by far the most burdensome disorder of all diseases in terms of disability-adjusted life-years[4,5].

Despite the availability of many antidepressants, the European Medicines Agency (EMA) has highlighted the need for novel medicines with better efficacy and safety profiles[6]. To this end, recent randomized, placebo-controlled clinical trials have demonstrated the efficacy and tolerability of an antidepressant with a different mechanism of action, vortioxetine[7,8]. Vortioxetine has a multimodal activity: direct modulation of receptor activity and inhibition of the serotonin (5-HT) transporter. *In vitro* studies indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and an inhibitor of the 5-HT transporter.

The development of novel treatment options presents a unique challenge, as MDD is a heterogeneous disease defined by symptoms, without any objective clinical laboratory diagnostic tests. Furthermore, significant reductions in signal detection are attributed to changes in the clinical trial environment, including expectation bias in both patients and investigators, as well as the inclusion of patients who might not be appropriate for the trial[9,10]. This leads to high response rates in the placebo control groups of randomized controlled trials (RCTs), increasing the difficulty of demonstrating a therapeutic benefit. Indeed, $\geq$50% of RCTs using recently approved antidepressants failed due to high placebo responses[11,12]. Despite this, vortioxetine has proven to be efficacious in the treatment of MDD in the majority of trials, whilst also showing good tolerability[7,8,13–18]. Vortioxetine has been approved in the United States by the Food and Drug Administration (FDA) for the treatment of adult patients with MDD and by the European Medicines Agency (EMA) for the treatment of adult patients with major depressive episodes.

Health Technology Assessment (HTA) requires the comparison of a novel drug against a broad range of marketed comparators to ensure that the therapies with the most favorable benefit/risk profile reach patients and that limited healthcare resources are appropriately invested. Generation of comparative data can be associated with certain challenges. Statistical methods have their limitations and different methods can be used to compare multiple interventions. The potential variability between different reviews can be due not only to study selection but also to the evaluated outcomes (e.g. difference on a scale or categorical outcomes such as response or remission). A further limitation is publication bias, which results in the outcomes from failed studies not being available in peer-reviewed journals. This has been overcome, at least since 2007, by the requirement to register all controlled phase 2 and phase 3 clinical trials, and to publish the results from such trials of marketed pharmaceuticals. In addition, details of unpublished trials have been made freely available by individual pharmaceutical companies, or released by the EMA and published in review articles.

Patient selection bias can be introduced to trials when an experimental drug is tested alongside an active reference to confirm assay sensitivity, as recognized by the EMA[19]. For example, patients who were non-responsive to the active reference are always excluded for ethical reasons. We also expect that patients with prior exposure to the active reference may decline to participate due to previous poor response[20]. In an equipoise study comparing four drugs in schizophrenia, patients could opt to be randomized to only two or three drugs of their choice (among the four included in the study) based on their prior experience with the treatments; it was reported that 83% of the patients would have refused to participate in the study if they could have been randomized to any of the four drugs, which highlighted that negative experience with previous treatment has an important influence on patient participation and inclusion in clinical trials[20]. Studies using an active reference can also be biased when patients and investigators expect a certain response, in terms of efficacy and safety, to a marketed drug[21,22].

When there is a lack of unbiased head-to-head data, indirect comparisons can be viewed as an analytical tool to assess the comparative efficacy of a broad range of comparators, according to HTA requirements[23]. However, published randomized controlled trials (RCTs) often differ from one another in many aspects, including study design (placebo controlled, study length, dosage, evaluation of efficacy outcomes, time to primary endpoint) and patient population (indication, severity, duration of the current episode, number of prior episodes, treatment resistance, psychosocial stressors, suicidality, comorbidities, specific symptoms). Unfortunately, many of these baseline characteristics are rarely published.

Asymmetry in drug exposure over time can introduce further bias to comparative effectiveness research[24]. A study using mixed treatment comparisons has shown that the efficacy and acceptability of escitalopram improved over time. This was attributed to the enrolment of patients with more severe symptomatology in the most recent studies[25]. Indeed, later studies can often be designed with

substantial foreknowledge of how a drug is likely to act and in which subgroup of patients it is likely to have the best efficacy based on information from previous clinical use. In general, later trials are more likely to use an optimal dose and more specific patient inclusion and exclusion criteria. This again makes it essential to only compare novel drugs to marketed drugs using similarly designed trials (same study objective, homogeneity in study population), for example, only registration studies. Therefore, in the main analyses, this paper examines the relative efficacy and tolerability of vortioxetine versus marketed antidepressants using indirect treatment comparisons from registration, double-blind, randomized and placebo-controlled studies from their respective clinical development programs.

The aims of this paper are to describe the relative efficacy and tolerability of vortioxetine on MDD after 2 months of treatment, compared with the following marketed antidepressants: agomelatine (melatonergic agonism [MT_1 and MT_2 receptors] and 5-HT_{2C} antagonism, approved in Europe in 2009, not approved in the US), desvenlafaxine (approved 2008), duloxetine, escitalopram, sertraline, venlafaxine and vilazodone (serotonin reuptake inhibition and 5-HT_{1A} receptor partial agonism, launched 2011). The pharmacological profiles of vortioxetine, vilazodone and agomelatine differ from the selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs).

Materials and methods

Indirect comparison approach

This analysis used an indirect comparison meta-regression approach, an extension of classical random-effects meta-analysis, to compare vortioxetine to seven marketed antidepressants with four different mechanisms of action[26]. In this model, the estimated treatment effects from individual studies, directly comparing intervention to placebo, were regressed on the active treatment at the study level. The strength of meta-regression is that this method can then be used to investigate the influence of other covariates, such as age and gender, on the relative treatment effect.

Antidepressants evaluated

Due to the huge number of approved antidepressants (>30) we have chosen to limit the present analysis to comparing vortioxetine with the commonly used SSRIs and SSNIs as well as some recently approved antidepressants. Selected antidepressants included duloxetine and venlafaxine (both instant release [IR] and extended release [XR]) as widely used SNRIs and escitalopram and sertraline as SSRIs. The rationale for choosing duloxetine, venlafaxine, sertraline and escitalopram as their class representatives is because they were highlighted in the recent paper by Cipriani *et al.* as having the best acceptability, whilst also maintaining good efficacy[27]. Agomelatine, desvenlafaxine and vilazodone were included because they were recently launched. It should be noted that, due to its multimodal activity, vortioxetine has a different mechanism of action from all selected comparators. Tricyclic antidepressants (TCAs) were not included as, due to their benefit/risk profile, they are used in a different patient population. Other SSRIs, such as fluoxetine, were ranked lower than escitalopram, sertraline or venlafaxine in the Cipriani analysis and so further indirect comparisons with these agents would bring only minor incremental value.

Study selection

Clinical trials for the selected antidepressants were identified through a systematic review of published data, a database of RCTs created via systematic review (study extraction protocol available upon request) and the clinical registers of trial sponsors. Studies were identified by searching MEDLINE, Embase, Cochrane Central Register of Controlled Trials and PsychINFO. The following conference proceedings were hand searched: American Psychiatry Association (APA), European College of Neuropsychopharmacology (ECNP), International College of Neuropsychopharmacology (CINP), New Clinical Drug Evaluation unit (NCDEU) with the following registries: Clinicaltrials.gov, Clinicalstudyresults.org, Lundbecktrials.com, Forestclinicaltrials.com, Lillytrials.com, Novartis register, EMEA websites for retrieving the European Public Assessment Reports (EPAR) and FDA websites. Inclusion criteria consisted of RCTs in MDD, documented random assignment to treatment under double-blind conditions, assessing the licensed doses of agomelatine, desvenlafaxine, duloxetine, escitalopram, sertraline, venlafaxine and vilazodone with a placebo-controlled arm, with a primary efficacy outcome including the Montgomery–Åsberg Depression Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D) after 2 months of treatment (6–12 weeks). Studies had to enroll adult patients (≥18 years old). No time limit was applied to this literature review that was conducted in July 2011, but only articles in English were selected. The following studies were excluded: subgroup analyses, relapse- or recurrence-prevention studies and studies with fewer than 30 patients per treatment group.

All registration studies for vortioxetine that met the inclusion criteria were selected. To allow for accurate analysis, only studies testing an antidepressant (as an experimental drug) at a dose equal to the recommended dose or including doses within the licensed dose range (Table 1), alongside a placebo control, were included. The dose

Table 1. Dose range for antidepressants in major depressive disorder.

Antidepressant	Dose range*
Agomelatine	25–50 mg/day
Desvenlafaxine	50–400 mg/day
Duloxetine	60–120 mg/day
Escitalopram	10–20 mg/day
Sertraline	50–200 mg/day
Venlafaxine IR	37.5–375 mg/day
Venlafaxine XR	75–375 mg/day
Vilazodone	10–40 mg/day
Vortioxetine	5–20 mg/day

*According to Summary of Product Characteristics or Product Monograph.

selection for vortioxetine was 5 to 20 mg (Tables 1 and 2). When studies included an active reference to confirm assay sensitivity, data from this active reference arm were not included in the present analyses because of the previously detailed patient selection bias.

Furthermore, trials must have had treatment of depressive symptoms as their primary outcome. All studies identified used either the MADRS[97] or HAM-D[98] as the primary measure of depression. To ensure that studies included in the comparison were as similar as possible, studies were excluded if they had been designed for relapse prevention objectives or specified concomitant disease as an inclusion criteria.

The pool of studies was limited to registration studies in the primary analyses. In sensitivity analyses it was extended to post-marketing authorization studies that evaluated the drug of interest as an experimental intervention rather than as an active reference. The reason for this selection was that experimental interventions were deemed to have reached the market recently enough at the time trials were conducted so that the previously detailed patient selection bias would only have minimal impact, whilst active references would be more subject to it due to the number of patients previously treated with these drugs. Post-marketing authorization studies were considered to be those in which the first patient's first visit occurred after the drug's approval.

Outcomes

The two main outcomes of the present analysis were efficacy and tolerability. To enable comparisons between studies using different primary scales, MADRS or HAM-D (either HAM-D 17, 21 or 24) scores, the mean difference between the experimental drug and the placebo in the change from baseline to 2 months was standardized using the standard deviation of the treatment effect in each study. The study duration could vary from 6 to 12 weeks; where data from multiple time points were available, evaluation of endpoints closest to 8 weeks were preferentially included. The standardized mean differences (SMDs) were used as the dependent variable in the analysis.

The second outcome, tolerability, was defined as the proportion of total patients in each treatment group that withdrew from the study before completion due to adverse events (AEs) during the first 2 months (6–12 weeks) of treatment. The difference from placebo was measured as the odds ratio (OR) between active treatment and placebo. This OR computation for tolerability also included a small continuity correction to reduce the estimator bias and prevent problems with small numbers of events[99].

In trials with multiple doses of a single intervention, the data for different doses were pooled prior to the analysis, in accordance with standard practices[27]. Sensitivity analyses were conducted on endpoints of response and remission at 2 months.

Data extraction

The extraction of data from RCTs was carried out in parallel by two independent reviewers. Extraction grids were then compared and any discrepancies resolved by common examination of source documents. Many of the included study publications presented both observed case (OC) analyses and imputed last observation carried forward (LOCF) analyses. The LOCF imputation approach was used for binary efficacy outcomes, as the results for treatment response and remission were rarely published with the OC approach. For change from baseline to 2 months in continuous outcomes, results based on the OC approach were used preferentially. The use of LOCF is not optimal in the context of meta-regression, as this method favors treatment groups with lower withdrawal rates relative to placebo, whatever the absolute withdrawal rate of the treatment, particularly in the context of MDD[100]. In some studies a large imbalance in withdrawals was observed between the active treatment and placebo, not always in favor of placebo; this imbalance varies considerably between studies. Consequently, this imbalance at the study level can lead to the introduction of significant bias to the analysis. To accurately compare all treatments, it was considered that working on OC data was more adequate in the context of active-to-active indirect comparisons in MDD. Nevertheless, in the absence of OC summary statistics, LOCF summary statistics were considered. The mixed model for repeated measures (MMRM) approach was preferred over ANCOVA/ANOVA models for OC data since standard errors estimated by ANCOVA/ANOVA are less accurate than those estimated by MMRM, because they are based on observations at only one visit rather than all visits. Inaccurate standard errors can inflate the risk alpha and

Table 2. Characteristics of studies included in meta-analyses.

Active treatment	Study name	Treatment duration (weeks)	Doses (mg)	Trial size (number of pts)	Mean age (years)	Gender (% female)	BL mean in primary scale	Primary MDD scale	Pivotal study
Agomelatine[a]	Olie and Kasper[28,29]	6	25–50	238	45	74	27	HAM-D	YES
Agomelatine[a]	Kennedy and Emsley[29,30]	6	25–50	212	42	60	27	HAM-D	YES
Agomelatine[a]	Loo *et al.*[29,31]	8	25	276	42	67	27	HAM-D	YES
Agomelatine[a]	EU 2008 CL3-022[29]	6	25	282	43	69	28	HAM-D	YES
Agomelatine[a]	EU 2008 CL3-023[29]	6	25	279	41	75	26	HAM-D	YES
Agomelatine[a]	EU 2008 CL3-024[29]	6	25/50	607	41	73	27	HAM-D	YES
Agomelatine[b]	Stahl *et al.*[32,33]	8	25/50	503	43	65	27	HAM-D	YES
Agomelatine[b]	Zajecka *et al.*[33,34]	8	25/50	511	44	67	27	HAM-D	YES
Agomelatine[b]	CAG0178A2303[33]	8	25–50	335	42	64	27	HAM-D	YES
Desvenlafaxine	333[35,36]	8	50/100	325	45	70	24	HAM-D	YES
Desvenlafaxine[b]	Tourian *et al.*[36,37]	8	50/100	479	40	64	23	HAM-D	YES
Desvenlafaxine[b]	332[36,38]	8	50/100	474	43	59	23	HAM-D	YES
Desvenlafaxine[a]	309-EU[36,39]	8	200–400	241	45	69	25	HAM-D	YES
Desvenlafaxine[b]	317-US[36,39]	8	200–400	248	40	64	25	HAM-D	YES
Desvenlafaxine	3151A1-3359[40,41]	8	50	472	39	56	23	HAM-D	NO
Desvenlafaxine	3151A1-4415[42]	12	50	427	43	66	NA	HAM-D	NO
Desvenlafaxine[b]	3151A1-3362[43,44]	8	50	454	43	61	23	HAM-D	NO
Desvenlafaxine	223-FR/PL/US/ZA[36,45]	8	200/400	229	NA	NA	22	HAM-D	YES
Desvenlafaxine[b]	304-US[36,46]	8	100–200	247	41	60	24	HAM-D	YES
Desvenlafaxine[b]	306-US[36,47]	8	100/200/400	480	40	62	23	HAM-D	YES
Desvenlafaxine[a]	308-EU/WW[48]	8	200/400	375	45	66	25	HAM-D	YES
Desvenlafaxine[b]	320-US[49]	8	200–400	244	38	66	23	HAM-D	YES
Duloxetine	Detke *et al.*[50,51]	9	60	267	41	69	20	HAM-D	YES
Duloxetine[b]	Detke[50,52]	9	60	245	42	66	21	HAM-D	YES
Duloxetine[b]	F1J-US-HMCR[53,54]	8	60	410	42	63	18	HAM-D	YES
Duloxetine	F1J-MC-HMAYa[55,56]	8	80/120	281	44	74	20	HAM-D	YES
Duloxetine[b]	F1J-MC-HMATb[57,58]	8	80	180	41	63	18	HAM-D	YES
Duloxetine[b]	F1J-MC-HMATa[59]	8	80	174	43	63	18	HAM-D	YES
Duloxetine[b]	F1J-MC-HMAQa[60]	8	40–120	140	42	66	19	HAM-D	YES
Duloxetine[b]	F1J-MC-HMAQb[61]	8	40–120	157	41	68	18	HAM-D	YES
Duloxetine	F1J-MC-HMAYb[62]	8	80/120	295	45	69	21	HAM-D	YES
Escitalopram[b]	Bose *et al.*[63,64]	12	10–20	267	68	59	29	MADRS	NO
Escitalopram[b]	Burke *et al.*[65–67]	8	10/20	379	40	66	29	MADRS	YES
Escitalopram	Lepola *et al.*[67–69]	8	10–20	310	43	73	29	MADRS	YES
Escitalopram	Wade *et al.*[67,70,71]	8	10	380	40	76	29	MADRS	YES
Escitalopram[b]	SCT-MD-02[67,72]	8	10–20	258	42	55	29	MADRS	YES
Escitalopram[b]	SCT-MD-27[73]	8	10–20	409	40	56	30	MADRS	NO
Sertraline	Lydiard *et al.*[74]	8	50–200	261	41	66	22	HAM-D	NO
Sertraline[b]	Schneider *et al.*[75]	8	50–100	747	70	56	21	HAM-D	NO
Sertraline[b]	Stahl[76]	8	50–150	216	38	64	26	HAM-D	NO
Sertraline	Fabre *et al.*[77,78]	6	50/100/200	369	38	53	25	HAM-D	YES
Sertraline	Reimherr *et al.*[78,79]	8	50–200	299	40	53	23	HAM-D	YES
Sertraline[a]	SCT-MD-27[73]	8	50–200	409	40	56	30	MADRS	NO
Sertraline[b]	315 study[78]	8	50–200	165	42	72	23	HAM-D	YES
Venlafaxine IR[b]	Rudolph *et al.*[80,81]	6	75/225/375	358	43	39	26	HAM-D	YES
Venlafaxine IR[b]	Schatzberg and Roose[82]	8	37.5–225	200	71	51	23	HAM-D	NO
Venlafaxine IR[b]	Schweizer *et al.*[81,83]	6	25–75	151	41	69	25	HAM-D	YES
Venlafaxine IR[b]	EPIC 014 study[84]	6	75–225	204	40	60	24	HAM-D	NO

Table 2. Continued

Active treatment	Study name	Treatment duration (weeks)	Doses (mg)	Trial size (number of pts)	Mean age (years)	Gender (% female)	BL mean in primary scale	Primary MDD scale	Pivotal study
Venlafaxine IR	Cunningham *et al.*[81,84]	6	25–200	150	41	65	25	HAM-D	YES
Venlafaxine IR	600A-303[81]	6	Unknown	165	38	68	24	HAM-D	YES
Venlafaxine IR	600A-313[81]	6	75/200	237	38	66	25	HAM-D	YES
Venlafaxine XR	Cunningham[85,86]	8	75–150	293	41	63	24	HAM-D	YES
Venlafaxine XR	Rudolph and Feiger[87]	8	75–225	198	40	68	25	HAM-D	NO
Venlafaxine XR	Thase[86,88]	8	75–225	197	41	61	24	HAM-D	YES
Venlafaxine XR[a]	Study 367[86]	8	75/150	248	45	67	27	HAM-D	YES
Vilazodone	Khan *et al.*[89–91]	8	40	481	42	56	32	MADRS	YES
Vilazodone	Rickels *et al.*[90–92]	8	40	410	40	63	31	MADRS	YES
Vilazodone	EMD-68-843-009[91]	8	20–100	192	NA	NA	24	HAM-D	YES
Vilazodone	EMD-68-843-010[91]	8	40–60/80–100	289	NA	NA	24	HAM-D	YES
Vortioxetine	NCT00839423[13]	8	5/10	315	43	63	34	MADRS	YES
Vortioxetine	NCT00635219[93]	8	5/10	464	45	68	32	MADRS	YES
Vortioxetine	NCT00811252[8]	6	5	302	71	66	29	HAM-D	YES
Vortioxetine	NCT01140906[94]	8	15/20	461	47	66	31	MADRS	YES
Vortioxetine	NCT00672958[17]	6	5	600	42	58	32	HAM-D	YES
Vortioxetine	NCT00672620[15]	8	5	306	43	63	29	HAM-D	YES
Vortioxetine	NCT00735709[7]	8	5/10	420	46	63	33	HAM-D	YES
Vortioxetine	NCT01153009[95]	8	15/20	462	43	74	32	MADRS	YES
Vortioxetine	NCT01163266[96]	8	10/20	462	43	73	32	MADRS	YES
Vortioxetine	T21004-317[18]	8	10/15	469	45	70	34	MADRS	YES

Studies were carried out in [a]Europe, [b]US; those unmarked were carried out in multiple locations or data were unavailable.
HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery–Åsberg Depression Scale; NA: not available; pts: patients; BL: baseline; MDD: Major Depressive Disorder.

increase the likelihood of significant treatment differences being observed by chance[101]. Nevertheless, in the absence of MMRM results, ANCOVA/ANOVA results were considered.

Statistical analyses

Meta-analyses were first performed to estimate the combined difference between each treatment and placebo in terms of efficacy and tolerability outcomes. A random-effects model was used, as it can handle a certain amount of between-study heterogeneity and, in the presence of significant heterogeneity, gives more conservative results than does a fixed-effect model[102,103]. The combined effect was calculated as the weighted mean of the effects observed in each study, with the weights inversely proportional to the within-trial and between-trial variances[102]. Heterogeneity was assessed using both the Cochran's Q heterogeneity and associated p-value, and the I^2 statistic.

Although this first step did not directly inform the comparative efficacy and tolerability between active treatments, it ensures transparency by presenting results from all studies included in this review. Furthermore, these analyses also allowed consistency between the observed treatment effect from the meta-analyses and the estimated treatment effect from the indirect comparisons with meta-regression to be verified.

However, classical meta-analyses cannot provide an estimate of treatment effect versus comparators that were not assessed in the same study and so an extension of this method, meta-regression analysis, was used to perform an indirect comparison and estimate the difference between active treatments[102,104]. In this second step, treatment comparisons were conducted using a random-effects meta-regression model, allowing the treatment effect to vary between studies. This model is recommended in the presence of heterogeneity; if there is no heterogeneity, the model provides results similar to the fixed-effect model. The primary analysis model was as follows:

$$y_i = \beta_0 + \beta_1 x_i + u_i + \varepsilon_i \quad \text{where } u_i \sim N(0,\tau^2) \text{ and } \varepsilon_i \sim N(0,\sigma_i^2)$$

y_i : *SMD or log odds ratio versus placebo in study i*

β_0 : *intercept to be estimated*

β_1 : *treatment coefficient to be estimated*

x_i : *the active treatment in study i (vortioxetine or a specified comparator)*

u_i : *between – study error term random effect*

ε_i : *within study error term random effect*

τ^2 : *the between – trial variance*

σ_i^2 : *the within – trial residual variance in study i*

Each trial is given a weight inversely proportional to the within-trial variance and the residual between-trial variance. The residual maximum likelihood method was used to estimate the between-trial variance.

Sensitivity analyses

Following previously published meta-regression analyses[27,104], further adjustments with covariates were introduced into the meta-regression model in sensitivity analyses. This allowed the investigation of whether variables other than treatment influenced the observed between-treatment differences. The potential adjustment covariates examined were age and gender. Post-marketing authorization studies were included according to the inclusion and exclusion criteria to assess the robustness of the results.

Additional analyses were conducted on other endpoints, including response (≥50% reduction in score) and remission (defined as reported in source documents), and using LOCF imputation for the change from baseline to 2 months.

Statistical software

Meta-analyses were performed using RevMan software (Review Manager [RevMan]) and meta-regressions were performed using the metareg package from STATA software (STATA/SE 10)[105]. All data management was performed using SAS. All analyses were performed by one statistician and quality control was conducted by another. Results from analyses were then compared and any discrepancies in the analyses were resolved by program examination by the statisticians.

Results

Studies selected

Using the search criteria described above, a total of 117 studies were identified as potentially relevant for the analyses. Of these, 57 studies were selected for the primary analyses on efficacy and tolerability, including 10 vortioxetine studies and 47 with other antidepressants (Figure 1). The primary set of studies included a total of 18,326 patients with a mean age of 43 years; of these, 65% were women. These studies had durations of 6 to 9 weeks, with a mean length to efficacy endpoint of 7.6 weeks (23% of studies with endpoint at 6 weeks, 74% at 8 weeks and 3% at 9 weeks) and included an average of 322 enrolled patients per study. The MADRS scale was used as the primary endpoint in 21% of trials and HAM-D in 79%. Trial characteristics are shown in Table 2.

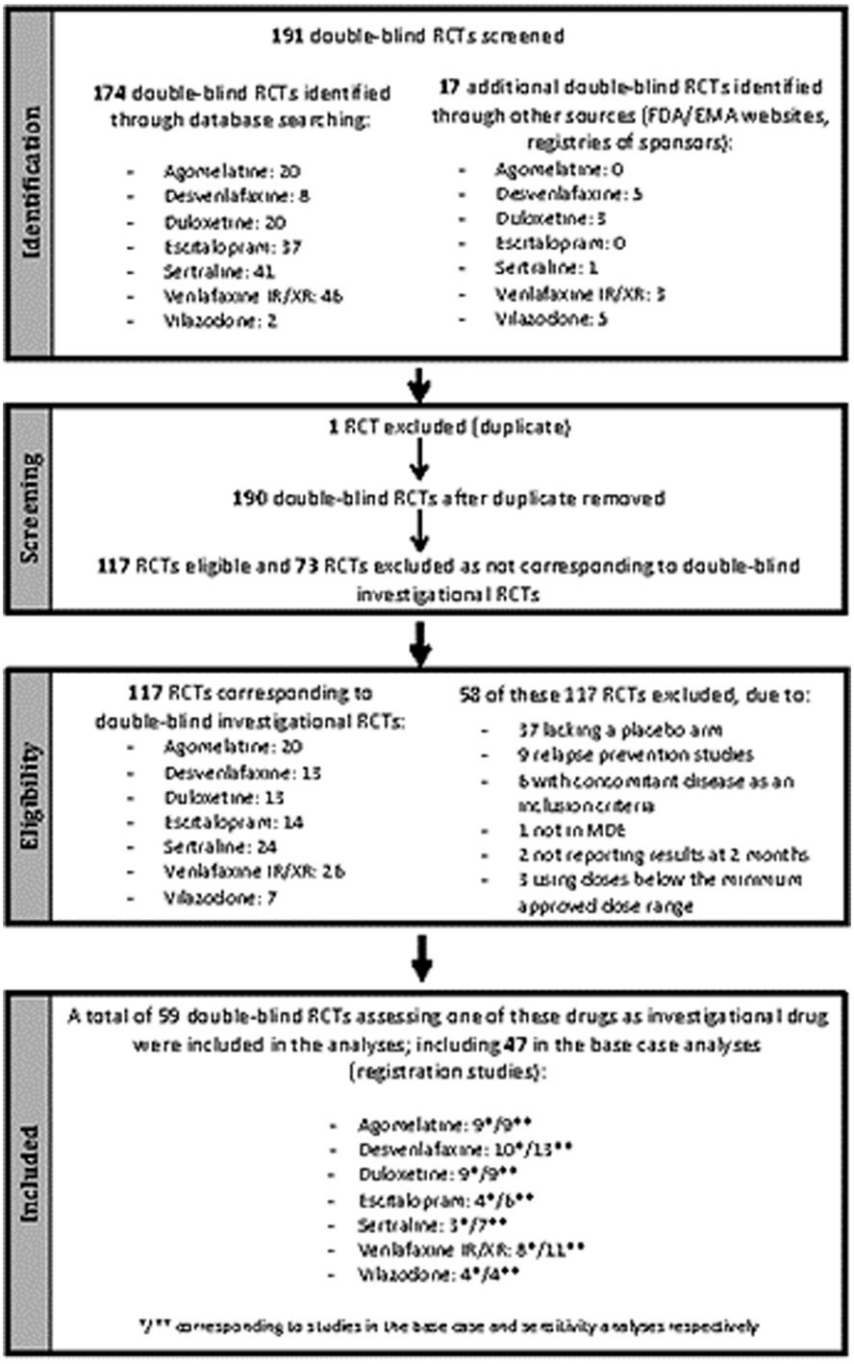


Figure 1. Selection of studies for meta-regression analyses.

Meta-analyses

Meta-analyses were performed, comparing the antidepressant investigated against the placebo control for both the primary efficacy scale (Figure 2) and for withdrawals due to any AE (Figure 3). All antidepressants except vilazodone showed a statistically significant beneficial efficacy effect versus placebo. Placebo was shown to have a statistically significant lower rate of withdrawal due to AEs than all antidepressants except for agomelatine.

Meta-regression analyses

Meta-regression analyses estimated the treatment effect for the primary efficacy scale (Figure 4) and for tolerability

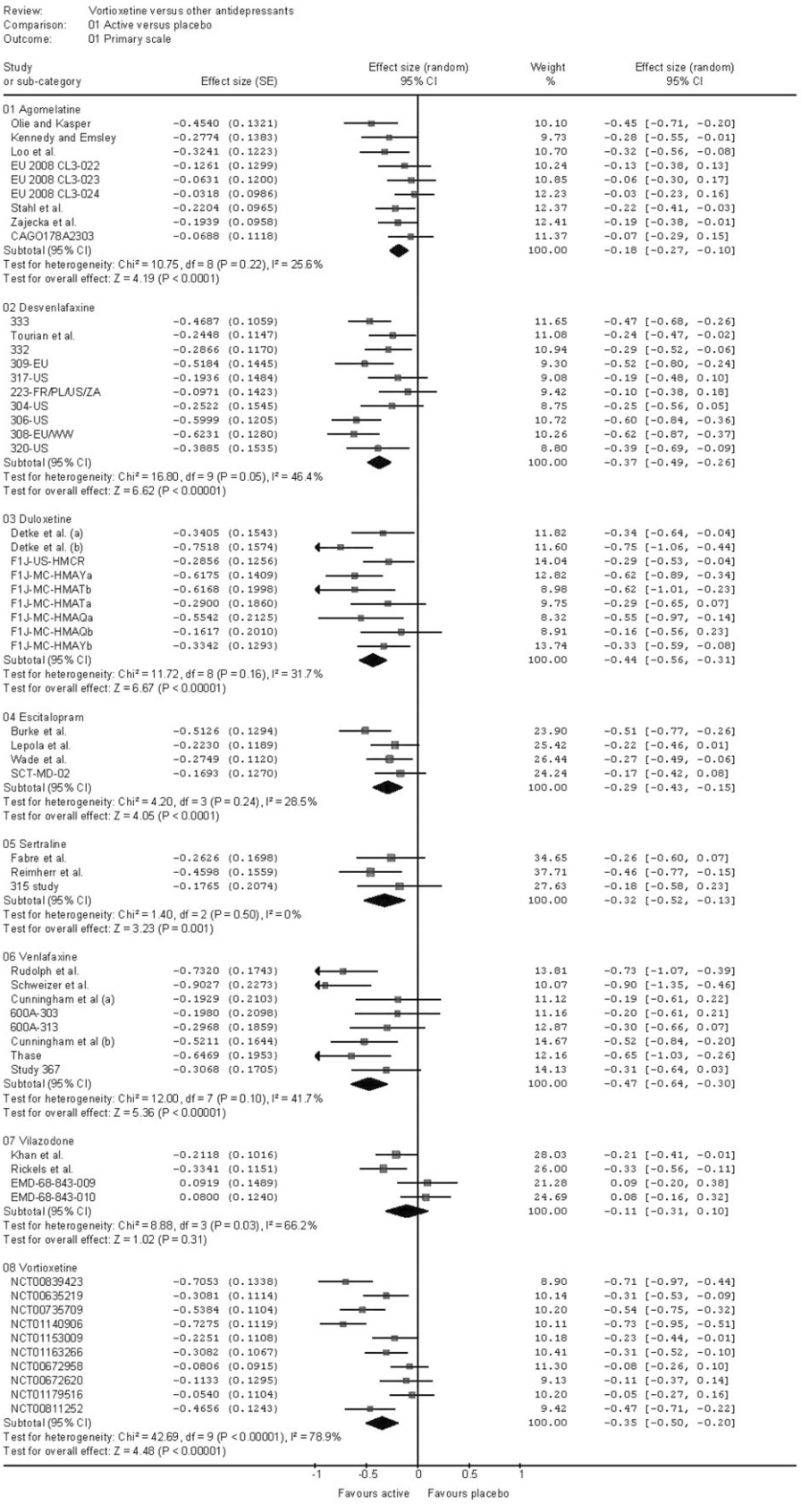


Figure 2. Meta-analyses for all antidepressants versus placebo; primary efficacy scale (standardized effect size). Studies are described in Table 2 (with corresponding reference number).

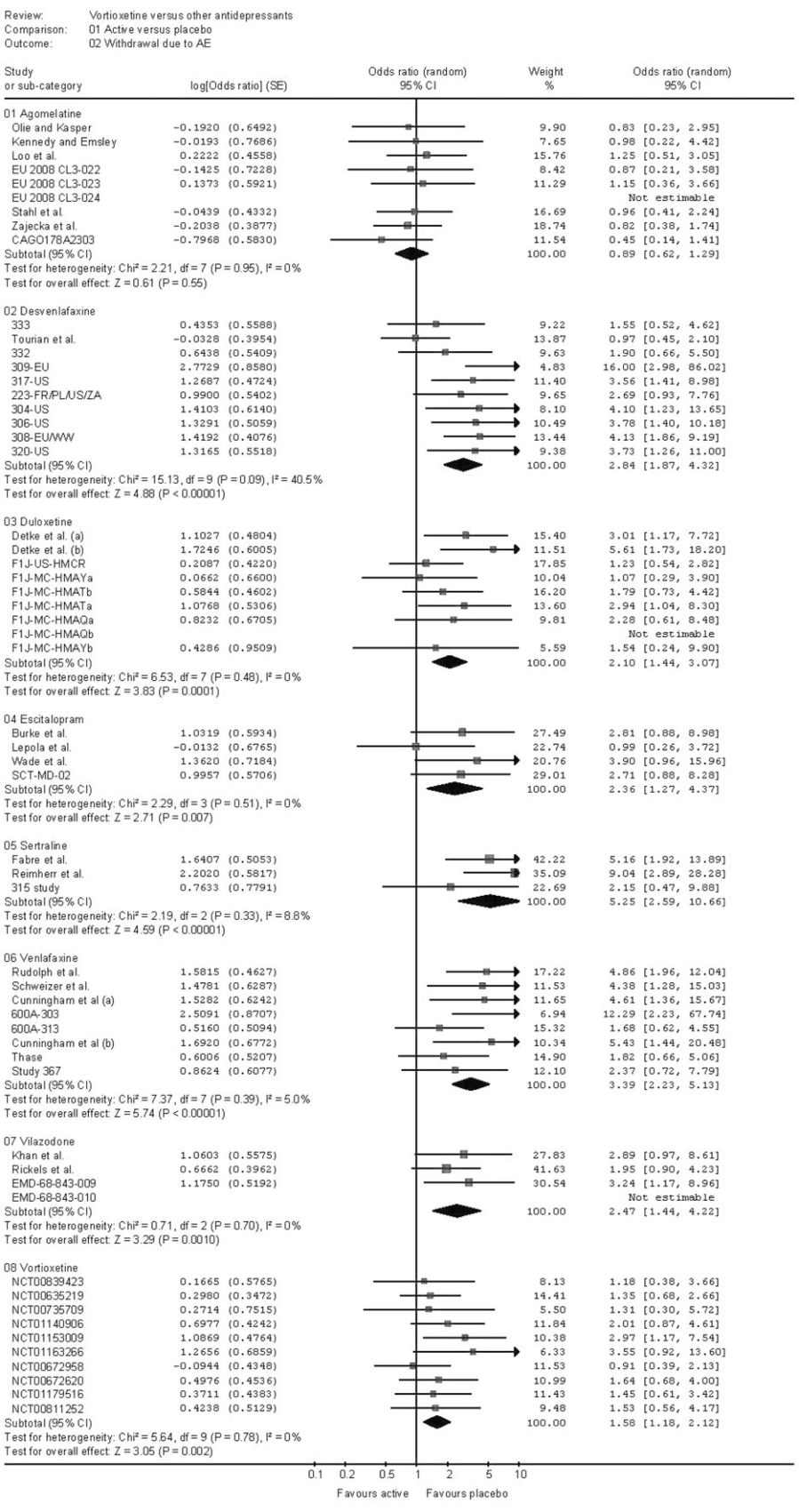


Figure 3. Meta-analyses for all antidepressants versus placebo; withdrawals due to any adverse event. Studies are described in Table 2 (with corresponding reference number).

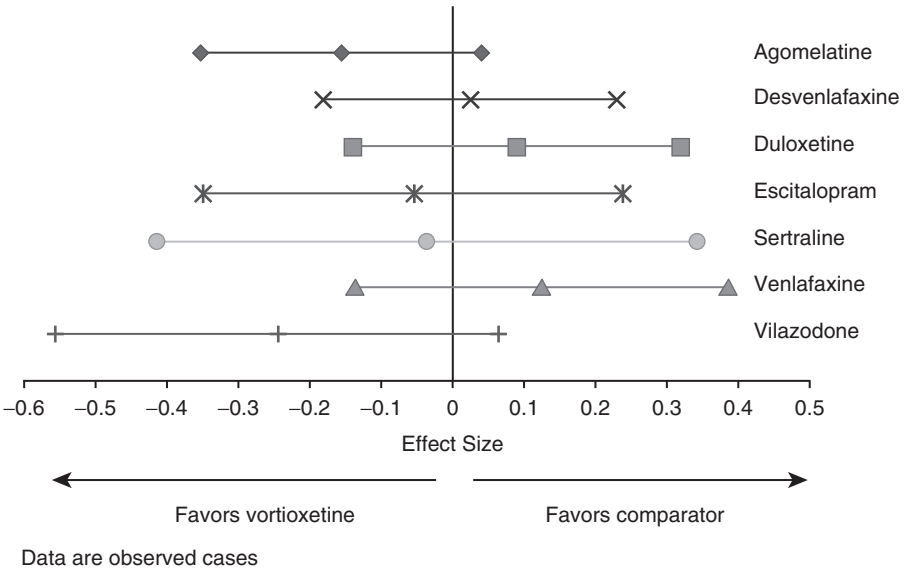


Figure 4. Difference between vortioxetine and comparators; treatment effect estimates for change from baseline on the primary scale at 2 months.

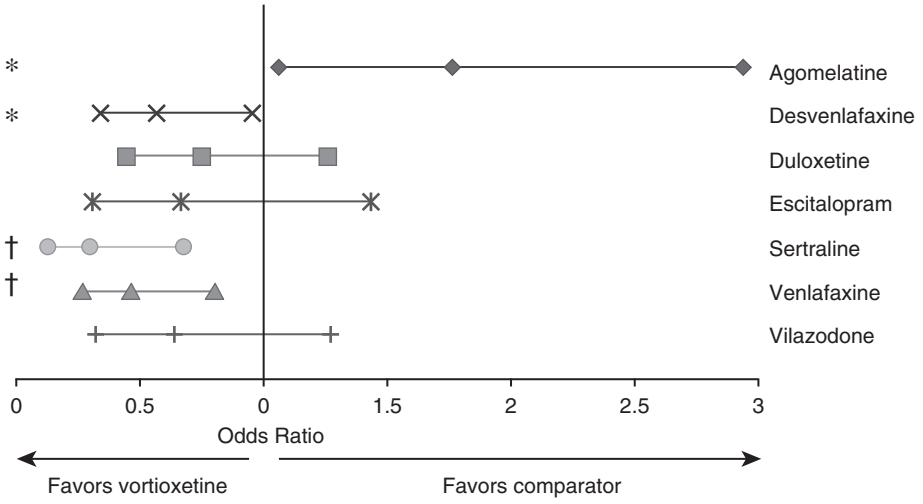


Figure 5. Difference between vortioxetine and comparators; odds ratios of withdrawals due to any adverse event over 2 months.

(Figure 5), for vortioxetine versus comparators. These data reveal that the efficacy of vortioxetine, as measured by MADRS or HAM-D score, is comparable to the efficacy of other antidepressants and has a favorable tolerability profile compared to desvenlafaxine, sertraline and venlafaxine. The estimated treatment effect for efficacy is numerically in favor of vortioxetine compared to four of the seven antidepressants analyzed (Figure 4). However, none of the differences in efficacy reached statistical significance and are also unlikely to be clinically relevant.

For the tolerability analyses, two groups of antidepressants were observed (Table 3). The first included desvenlafaxine, sertraline and venlafaxine, which had an incidence of withdrawal due to any AE >11.0% (Table 3); high doses of desvenlafaxine (200–400 mg) skewed its overall incidence to the right-hand side of the graph (data not shown). The second included the other four antidepressants, which had incidences ranging from 4.39% to 8.52%. Vortioxetine had favorable tolerability, with a mean AE withdrawal rate of 6.50%. The differences in tolerability between vortioxetine and

Table 3. Weighted mean incidence of withdrawals for any adverse event.

	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone	Vortioxetine
Weighted mean incidence of withdrawals for any adverse event	4.39%	11.04%	8.50%	5.77%	17.38%	17.62%	8.52%	6.50%

the first group were statistically significant in favor of vortioxetine (OR 0.58 [$p<0.05$] versus desvenlafaxine; OR 0.30 [$p<0.01$] versus sertraline; OR 0.47 [$p<0.01$] versus venlafaxine IR/XR). Agomelatine, with a mean incidence of withdrawals due to any AE of 4.4%, had a statistically significant advantage compared to vortioxetine (OR 1.77 [$p<0.05$]).

Sensitivity analyses

Several sensitivity analyses were carried out to determine whether differences observed between treatment groups in the primary analyses were reliable. The reliability of these results was first assessed by the inclusion of post-marketing authorization studies, second by using LOCF imputation for the change from baseline to 2 months for all studies, third by adjusting the treatment effect for an imbalance in age and gender across studies, and finally by investigating efficacy on two additional outcomes, treatment response and remission at 2 months.

The selection of studies for the primary analyses excluded any post-marketing authorization studies. These were considered for the first sensitivity analysis, resulting in the addition of three studies for desvenlafaxine, two for escitalopram, four for sertraline and three for venlafaxine IR/XR.

In all instances the sensitivity analyses for efficacy and tolerability agreed with the conclusions of the primary analyses (Table 4). Adjustment on mean age and on proportion of women in each study produced results which were very close to those of the primary analyses. Similar observations were made with adjustments using LOCF.

A high number of studies included in the primary analyses have missing data for response and remission endpoints. There are no published data for three studies for agomelatine (out of nine), four studies for venlafaxine (out of eight), one study for escitalopram (out of four), two studies for sertraline (out of three) and two studies for vilazodone (out of four). Sensitivity analyses on response and remission confirmed the primary efficacy analyses for duloxetine and desvenlafaxine, the only treatments with a relatively low number of studies with missing data (Table 4).

Discussion

Based on the assessment of studies in their respective registration programs, the meta-regression results presented here indicate that vortioxetine is comparable in efficacy to other marketed antidepressants, as measured by MADRS or HAM-D score, and has a favorable tolerability compared to desvenlafaxine, sertraline and venlafaxine. This is an important balance showing that vortioxetine offers a favorable combination of efficacy and tolerability versus other selected antidepressants, which is one of the factors that may encourage patient compliance.

Considering only those studies investigating treatment effect within similar experimental conditions increases the reliability of the treatment comparison. Only trials from each drug's MDD clinical development program were included. This reduces publication bias, which can arise when a marketed and non-marketed drug are compared. In addition, the RCTs considered here had similar patient populations (diagnosed MDD) and primary objectives (the treatment of depressive symptoms).

There are currently no published indirect comparisons of vortioxetine with other antidepressants, although this method has previously been used to compare other interventions included in this analysis[104]. The use of meta-regression to explain treatment effect heterogeneity has been proven valid and is often used in Cochrane reviews[106]. By selecting comparable studies we maximized the likelihood that the active treatment was the most likely explanation for the heterogeneity of the treatment effect across studies. If the active treatment did not explain heterogeneity, we could infer an absence of difference between the active treatments.

Meta-regression analyses carried out with adjustments for additional variables (age and gender) revealed that the differential treatment effects were consistent. Sensitivity analyses based on LOCF imputation confirmed these findings. For agomelatine, most of the published data are based on LOCF, with OC data only available for one study. In these studies, withdrawal rates in the placebo arm were sometimes higher than those seen with agomelatine treatment, which may bias the LOCF analysis in favor of agomelatine. For all other treatments, at least half the studies

Table 4. Results of the sensitivity analyses on treatment effect estimates for efficacy and tolerability.

Drug versus vortioxetine	Agomelatine	Desvenlafaxine	Duloxetine	Escitalopram	Sertraline	Venlafaxine	Vilazodone
Primary efficacy scale – effect size <0 favors vortioxetine							
Treatment effect estimate for efficacy change from baseline on the primary scale at 2 months (*p*-value)	−0.156 (0.113)	0.025 (0.803)	0.090 (0.419)	−0.054 (0.695)	−0.037 (0.832)	0.124 (0.328)	−0.245 (0.111)
Inclusion of post-marketing studies (*p*-value)	−0.156 (0.113)	−0.022 (0.804)	0.090 (0.419)	−0.064 (0.574)	−0.026 (0.807)	0.069 (0.526)	−0.245 (0.111)
Imputation data – LOCF (*p*-value)	−0.067 (0.404)	−0.024 (0.739)	0.061 (0.484)	0.046 (0.674)	0.040 (0.765)	0.135 (0.175)	−0.159 (0.197)
Adjustment by gender (*p*-value)	−0.147 (0.148)	0.056 (0.597)	0.091 (0.429)	−0.052 (0.721)	−0.104 (0.616)	0.080 (0.542)	−0.108 (0.636)
Adjustment by age (*p*-value)	−0.118 (0.245)	0.099 (0.360)	0.124 (0.300)	−0.017 (0.908)	0.015 (0.939)	0.170 (0.224)	−0.033 (0.867)
Withdrawals due to any AE – odds ratio <1 favors vortioxetine							
Treatment effect estimate for tolerability (*p*-value)	1.769 (0.030)	0.578 (0.035)	0.752 (0.262)	0.671 (0.275)	0.299 (0.008)	0.469 (0.009)	0.640 (0.181)
Inclusion of post-marketing studies (*p*-value)	1.769 (0.030)	0.701 (0.157)	0.752 (0.262)	0.742 (0.305)	0.497 (0.012)	0.461 (0.003)	0.640 (0.181)
Adjustment by gender (*p*-value)	1.849 (0.022)	0.518 (0.019)	0.735 (0.229)	0.664 (0.267)	0.247 (0.013)	0.455 (0.012)	0.532 (0.151)
Adjustment by age (*p*-value)	1.781 (0.035)	0.566 (0.061)	0.755 (0.299)	0.680 (0.312)	0.304 (0.014)	0.468 (0.014)	0.712 (0.390)
Response and remission – score >1 favors vortioxetine							
Primary scale response – LOCF (*p*-value)	1.045 (0.815)	1.153 (0.364)	0.893 (0.514)	0.843 (0.523)	0.772 (0.575)	0.789 (0.353)	0.975 (0.934)
Primary scale remission – LOCF (*p*-value)	1.220 (0.470)	1.029 (0.852)	0.894 (0.526)	0.990 (0.981)	NA	0.689 (0.444)	0.983 (0.952)

LOCF: last observation carried forward; NA: not available.

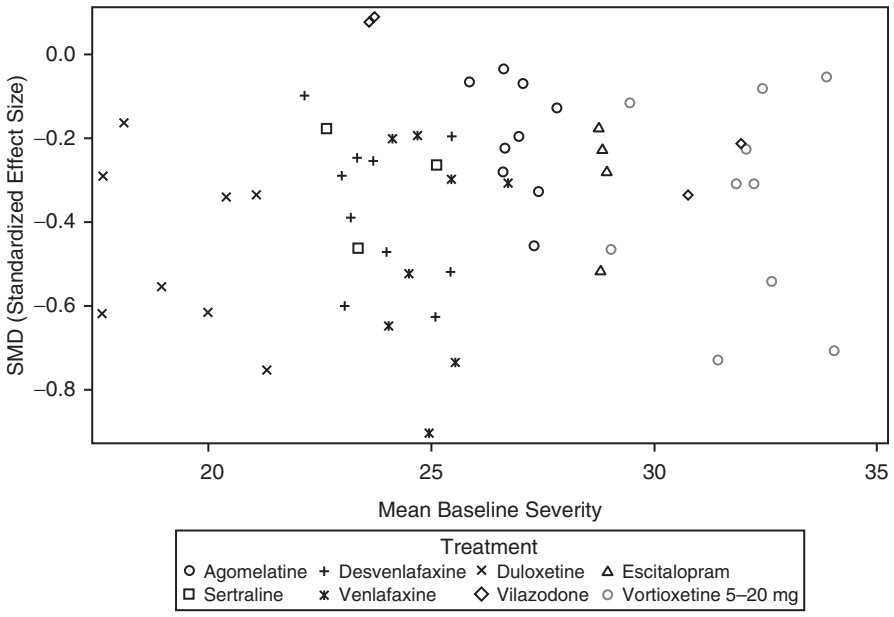
were reported in OC and did not require the use of LOCF data.

Sensitivity analyses including post-marketing trials did not alter the findings of the primary analyses. This is explained by the fact that six of 12 studies included were initiated in the year following market approval and, for some comparators, this sensitivity analysis coincided with the primary analysis due to the absence of post-approval studies satisfying the inclusion criteria.

Meta-regression analyses on treatment response and remission at 2 months were weakened by the high number of studies with missing data, i.e. studies that did not report response and/or remission results. This was particularly true in the case of failed studies (defined as studies with no statistical difference from placebo for the primary outcome), including three studies with missing data on response/remission for agomelatine (out of three failed studies); one study for escitalopram (out of one); one study for sertraline (out of two); three studies for venlafaxine (out of four) and two studies for vilazodone (out of two). For desvenlafaxine, remission data were missing from only one study, whilst response and remission data were available for all duloxetine and vortioxetine studies. For the two comparators with almost complete response and remission data, the estimated treatment effect of vortioxetine produced results consistent with those of the primary analyses.

Combining evidence from different measures of depression in the primary efficacy analyses allowed the improvement of estimate precision by considering all available data from studies satisfying the inclusion criteria. Standardized treatment effects were used to correct the heterogeneity in the different efficacy measures arising due to differences in the scale ranges and variances, in line with published recommendations[106]. Nevertheless, by using this approach, adjustments on baseline disease severity, measured in different scales across trials, were not possible without standardization. Unlike the standardization method used for treatment effect, no consensus on a common method of standardization is available for baseline mean severity. In order to ensure that this model does not suffer from lack of adjustment on mean baseline severity, the standardized effect size was plotted against the raw baseline severity to evaluate the potential presence of a linear relationship between the SMD and baseline severity (Figure 6). The scatterplot did not reveal evidence of any positive or negative relationship between the two variables for any of the treatments. The difference in the mean baseline severity of vilazodone does not explain the difference in the SMD because the two sets of studies used two different scales (HAM-D 17 and MADRS); when the data are rescaled, the difference in severity may disappear.

The large number of studies included in the meta-regression analyses supports its usefulness for clinical practice. The sole inclusion of primary endpoints from



Note: Different scales (MADRS/HAM-D) and different versions of the HAM-D scale (17, 21 and 24 items) are used for baseline severity.

Figure 6. Relationship between standardized mean differences and mean baseline severity.

registration studies in the primary analysis minimized publication bias arising from unreported failed studies, as primary endpoint results for registration studies are present in the authorities' review documents. Selection bias was also limited by the definition of standard and valid inclusion criteria for all studies.

Although Cipriani and colleagues' systematic review suggests the preferable use of response rate as a primary efficacy measure[27], it has been demonstrated that assessments based on response rates can inflate differences between treatments, and Schwan and Hallberg consequently recommend that comparison of efficacy between drugs based on overall change in the MADRS or HAM-D score is first required[107]. The choice of discontinuation rates in the Cipriani paper as a measure of tolerability or safety was criticized by Gartlehner *et al.* as liable to confounding by factors unrelated to tolerability[27,108]. In the current paper, the measure of tolerability was limited to the withdrawals due to AEs and not all-cause withdrawals. This is the only relevant outcome commonly published; thus to use other outcomes would have limited the number of eligible studies and the power of the present analysis. It is also noteworthy that there is very little between-study variability in the placebo-arm withdrawal rates due to AEs, suggesting that the differences observed are attributable to treatment differences. It is true, however, that the computation of relative tolerability based upon the proportion of patients withdrawing from the study due to AEs does not account for different types of AEs or their degree of severity.

In the future, to aid clinicians' choice of treatment, more parameters affecting the overall tolerability of a drug should be used as treatment differentiators, such as specific treatment-related AEs. Currently, the absence of these data in publications limits the possible analyses on these outcomes and the lack of power in these analyses prevents the detection of clinically significant differences between treatments. These analyses compare vortioxetine to only a limited selection of the available marketed antidepressants, but those included have previously been shown to be among the best in terms of efficacy and tolerability[27] and so set a high benchmark for comparative analysis. Additional factors that could impact treatment choice, such as ease of use (dosing frequency, titration requirements, need for taking with food, etc.), as well as access and cost were not included in the present analyses but should be considered by clinicians when determining the treatment to be prescribed to a given patient.

Covariate adjustment in meta-regression presents some limitation to this analysis, such as the ecological fallacy for covariates, which can occur when an inference for an individual patient is made using aggregate data from a group of individuals (e.g. mean age)[109]. Unknown aggregate confounders across comparators may exist, but in the context of MDD, no publications yet address this issue. To investigate the extent of this ecological fallacy in the MDD population, a consensus should be found to identify aggregated covariates (other than active treatment) that may have an impact on the treatment effect within a given clinical development program. The impact of duration of

the current episode, the number of prior episodes, geographical location and other population characteristics may be investigated as potential aggregate covariates explaining differences in response to treatment independently of the administered treatment itself. To enable these investigations there is a need for studies to report more data on patient baseline characteristics.

Despite some numerical differences, the present analyses did not reveal statistically significant differences in the efficacy of vortioxetine compared to other antidepressants, thereby supporting the view of a comparable efficacy as measured by MADRS or HAM-D score. Although in clinical practice differences in antidepressant response with different agents can be readily observed in individual patients, our findings are consistent with previous analyses that showed no substantial difference in clinical efficacy between antidepressants when comparing groups of patients[108]. However, it should be noted that both of these analyses rely heavily on the evidence collected in registration RCTs. In order to comply with regulatory requirements, these studies tend to include very similar patient populations (highly similar inclusion/exclusion criteria) and to use the same efficacy assessment scales (MADRS or HAM-D)[97,98].

Comparisons between vortioxetine and agomelatine demonstrate that differences can be observed between antidepressants in certain situations. Although the present analysis showed no significant difference in the efficacy of the two treatments, the REVIVE RCT (NCT01488071) has revealed that MDD patients randomized to either vortioxetine or agomelatine after an inadequate response to SSRIs or SNRIs could make significantly better improvements with vortioxetine than with agomelatine, demonstrating a differentiation between two treatments in this specific population of patients[110].

Although the MADRS and HAM-D are the most frequently used clinician-rated scales, they present some limitations. For example, MADRS has been criticized for putting 'all antidepressants into one basket' and HAM-D has been criticized for putting 'all depressions into one basket'. Therefore, the question as to whether a particular antidepressant could be more effective in a particular subtype of depression cannot be answered using these scales.

The present analyses demonstrated a favorable tolerability profile for vortioxetine by showing a significantly lower rate of withdrawals due to AEs, compared to several other antidepressants. This suggests that vortioxetine may also appeal to patients switching medication due to AEs, such as sexual dysfunction, which is an underreported, but important, AE of antidepressants[111,112]. Placebo-controlled trials have revealed that vortioxetine, at the recommended dose, has an incidence of sexual-dysfunction-related AEs comparable to that seen with placebo, whilst the active reference, either venlafaxine[13] or duloxetine[93], showed significantly more such AEs than placebo.

Finally, the comparison of antidepressants in this manuscript is based on statistical studies which relate to the average patient. However, in real life, the average patient does not exist[113], and it is therefore important to remember that the choice of a particular antidepressant needs to be tailored to match individual patient requirements. It is also noteworthy that all methods and analyses presented in this manuscript focus on the statistical significance of the differences between treatments, not on the clinical relevance of the aforementioned difference.

Conclusion

The comparison of a novel antidepressant with an approved drug may suffer from bias due to asymmetry in drug exposure over time. Consequently, indirect comparison with meta-regression is an appropriate alternative when studies included in such comparisons are selected to be comparable (similar design, patient population and primary outcome)[114]. Alternative methods like mixed-treatment comparison and inclusion of all randomized studies and active reference arms may provide complementary information to this analysis (more evidence, but also more heterogeneity).

The data presented here show that vortioxetine offers a comparable or favorable combination in terms of efficacy, as measured by MADRS or HAM-D score, and tolerability, as measured by withdrawal rate due to AEs, compared to other marketed antidepressants in placebo-controlled trials in the MDD population. With its different pharmacological profile, vortioxetine may help to tailor treatment to the requirements of the individual MDD patient. Further well designed head-to-head trials between vortioxetine and other antidepressant drugs are necessary to determine the place of vortioxetine in the management of MDD.

Transparency

Declaration of funding

This work was funded by H. Lundbeck A/S, the manufacturer of vortioxetine.

Declaration of financial/other relationships

P.-M.L. has disclosed that he has received grants from Lundbeck, Sevier and Lilly, and he is on the board of Sevier and Lundbeck. C.L. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article. M.B., B.R. and C.F. have disclosed they are employees of Lundbeck. S.S. has disclosed that he was an employee of Keyrus Biopharm during the time of the study, and provided statistical consultation to Lundbeck. L.E. has disclosed that he is an employee of PAREXEL International, a company that received funding from Lundbeck to conduct this study.

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