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REGULAR ARTICLE

Vortioxetine for depression in adults: A systematic review and dose–response meta-analysis of randomized controlled trials

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Aim: Major depressive disorder (MDD) is a prevalent psychiatric condition and vortioxetine offers promising antidepressant effects due to its unique pharmacological profile. However, the dose–response relationships of vortioxetine for MDD is not well established. We aimed to conduct dose–response meta-analyses to fill this gap.

Methods: We systematically searched multiple electronic databases for randomized controlled trials of vortioxetine for MDD, with the last search conducted on 08 February, 2024. The dose–response relationship was evaluated using a one-stage random-effects dose–response meta-analysis with restricted cubic spline model. The primary outcome was efficacy (mean change in depression scale score), with secondary outcomes including response, dropout for any reasons (acceptability), dropout for adverse events (tolerability), and any adverse events (safety).

Results: The dose–response meta-analysis comprised 16 studies, with 4,294 participants allocated to the vortioxetine group and 2,299 participants allocated to the placebo group. The estimated 50% effective dose was 4.37 mg/day, and the near-maximal effective dose (95% effective dose) was 17.93 mg/day. Visual inspection of the dose-efficacy curve suggests that a plateau possibly had not been reached yet at 20 mg/day. Acceptability, tolerability and safety decreased as the dose increased. Subgroup analysis indicated that no significant differences were observed in acceptability, tolerability and safety among the dosage groups.

Conclusions: Vortioxetine may potentially provide additional therapeutic benefits when exceeding the current licensed dosage without significantly impacting safety. Conducting clinical trials exceeding the current approved dosage appears necessary to fully comprehend its efficacy and risk.

Keywords: *dose–response relationships, efficacy, major depressive disorder, meta-analysis, vortioxetine.*

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Major depressive disorder (MDD) is a prevalent psychiatric condition characterized by persistent feelings of sadness, or loss of pleasure in daily activities, accompanied by other cognitive, behavioral, or neurovegetative symptoms,[1] affecting approximately 340 million people worldwide.[2] Depression imposes a heavy burden on individuals, families, and entire societies. Globally, it is one of the leading causes of disability-adjusted life years,[3] exacerbating the global disease burden and resulting in substantial healthcare expenditures.[4] Despite the availability of various pharmacological and psychotherapeutic interventions, a substantial proportion of patients (approximately one-third) with MDD fail to achieve adequate symptom relief with standard treatments alone.[5,6] This treatment-resistant nature of MDD underscores the need for novel therapeutic approaches that can effectively target depressive symptoms.

Vortioxetine is a novel multimodal antidepressant that has emerged as a promising option for the management of MDD.[7] Unlike traditional selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), vortioxetine exerts its antidepressant effects through a combination of serotonin reuptake inhibition, receptor modulation, and neuroplasticity enhancement.[8,9] The expression of brain derived neurotrophic factors (BDNF) mediates neuronal survival and brain neuroplasticity. Research has shown that in chronic unpredictable mild stress (CUMS)-induced depressive rats, the mean optical density value of hippocampal BDNF in the vortioxetine treatment group (CUMS+VOR) was significantly higher than that in the fluoxetine group (CUMS+FLU) and the vehicle treatment group (CUMS).[10] This indicated that long-term administration of vortioxetine, rather than fluoxetine, significantly increased hippocampal BDNF level compared with the CUMS group. Notably, vortioxetine not only alleviated depressive symptoms but also improved cognitive function in patients with MDD, as confirmed by several studies.[11,12] Additionally, research found an association between overall cognitive function and reward function in MDD receiving vortioxetine.[13] Specifically, individuals with higher cognitive performance showed greater effort for hard task rewards in MDD treated with vortioxetine. The unique pharmacological profile of vortioxetine makes it a compelling candidate for investigating the dose–response relationship in the treatment of depression. While the efficacy and safety of vortioxetine across a range of doses have been evaluated in clinical trials,[14–16] the character of the dose–response relationship remains incompletely understood.

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The dose–response meta-analysis (DRMA) provides an opportunity to synthesize data from multiple studies and construct dose–response curves using mathematical functions,[17,18] providing a comprehensive overview of the dose–response relationship of vortioxetine in MDD. Our study systematically analyzed the literature to identify the dose–response relationships of vortioxetine for MDD, aiming to provide information and guidance for clinical practice.

Methods

Search strategy

The study protocol has been registered in PROSPERO (CRD 42024510827) and adheres to the PRISMA 2020 statement for systematic review reporting.[19] We conducted a comprehensive search of EMBASE, PubMed, Web of Science, and the Cochrane Library from inception up until 8 February, 2024, without language restrictions. MeSH terms and keywords were used to generate the search strategy, which included terms such as depression, major depressive disorder, depressive disorder, depressed, vortioxetine, and Lu AA21004 (detailed search strategy can be found in Table S1). Additionally, we reviewed references of previously published systematic reviews and meta-analyses on vortioxetine to identify potential studies meeting our inclusion criteria. Two reviewers independently conducted the search and screened titles and abstracts. Any discrepancies were resolved through full-text analysis until consensus was reached between the two reviewers; if consensus could not be reached, a third reviewer made the final decision.

Inclusion criteria and study selection

We included randomized controlled trials meeting the following criteria:

(a) Participant: Adults aged 18 years and older diagnosed with MDD based on versions of the DSM or the SCID (e.g., DSM-IV, SCID-5).

(b) Intervention: Vortioxetine or Lu AA21004.

(c) Comparison: Placebo control or other antidepressants.

(d) Outcome: We included the following outcomes assessed after 6–8 weeks of treatment: (1) Primary outcomes: Change in Montgomery-Åsberg Depression Scale (MADRS)/Hamilton Depression Rating Scale (HAM-D) total score from baseline to the last visit (mean ± SD) between the intervention and control groups. Any other validated scale was used when these two scales were not available. (2) Secondary outcomes: Response (defined as a reduction of 50% or more in the total score on the scale for depression), dropout for any reason (as an overall measure of treatment acceptability), dropout due to adverse events (as an assessment of tolerability), and the rate of any adverse events (as a safety assessment).

(e) Study design: Only randomized controlled studies were included. For studies examining the dose–response relationship, we included all studies within the same trial comparing two or more fixed or flexible dose treatment groups (including placebo). There were no restrictions on the dose of vortioxetine in the included studies.

We excluded studies meeting any of the following criteria: (1) Patients under 18 or those with other psychiatric disorders (e.g., generalized anxiety disorder, social anxiety disorder, etc.); (2) studies not published in English; (3) studies lacking outcomes of interest to us.

Data extraction

The data extraction process was similar to our previously published meta-analysis.[20] Two researchers independently reviewed and extracted relevant data. It should be noted that if the necessary data were not fully described in the publication, we endeavored to extract the data from the provided figures using Engauge Digitizer software[21,22] or contact the corresponding author of the study. Relevant studies that lacked accessible data were excluded from our analysis.

Risk of bias assessment

Two reviewers independently assessed the risk of bias using the revised Cochrane risk-of-bias tool for randomized trials.[23] We evaluated the risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The risk of bias for each domain was categorized as low, unclear, or high. A study was classified as having low risk of bias if none of these domains were rated as high risk and three or fewer domains were rated as unclear risk; if none of the domains were rated as high risk but four or more were rated as unclear risk, it was classified as having a moderate risk of bias; all other situations were considered to have a high risk of bias.

Data analysis

We conducted data analysis following the Cochrane Intervention Review Handbook.[24] Meta-analysis was conducted using Stata/MP 17.0, while the DRMA was performed using R version 4.3.0. The mean and standard deviation (M ± SD) of continuous variables in both the experimental and control groups were either directly extracted or derived indirectly from the included studies. Standardized Mean Difference (SMD), utilizing Cohen's d, was employed to quantify effect sizes for continuous variables evaluated across disparate scales. A Cohen's d of 0.2 suggests a small effect, 0.5 indicates a moderate effect, and 0.8 signifies a large effect.[25] Binary data was analyzed using risk ratio (RR). We conducted individual meta-analyses comparing vortioxetine with placebo, SSRIs, and SNRIs, respectively. We used a random-effects model because the aim of the analysis was to generalize the findings to a larger population that includes all possible studies.[26] Performing subgroup analysis based on dosage to preliminarily investigate the dose response relationships of vortioxetine. The I^2 statistic was utilized to assess study heterogeneity, with values suggesting different levels of heterogeneity: 0%–40% indicating possibly insignificant, 30%–60% potentially moderate, 50%–90% possibly significant, and 75%–100% indicative of considerable heterogeneity. Furthermore, we employed a leave-one-out method for sensitivity analysis to assess the robustness of the primary meta-analysis results. Funnel plots and Egger's test were used to evaluate publication bias.[27]

We conducted DRMA using the "dosresmeta" package in R,[17,18] employing a one-stage restricted cubic spline regression model with knots at the 25th, 50th, and 75th percentiles. If the one-stage restricted cubic spline regression model failed to adequately fit the data, alternative models such as two-stage linear model were considered.[28] We estimated the 50% effective dose (ED50) and the near-maximal effective dose (95% effective dose) for the dose–response curve, as has been done in prior studies.[17,29] The ED50 represents the dose at which half of the maximal potential antidepressant effect of vortioxetine is expected, while the ED95 represents the dose at which 95% of the maximal potential effect is achieved. For studies with flexible dosing regimens, we used the median dose for analyzing MADRS/HAMD scores. For instance, if the flexible dose range was 10–20 mg/day, we used 15 mg as the analyzed dose. Maximum dose was utilized when analyzing the dose–response relationship for acceptability, tolerability, and safety.

For the dose–response relationship results, we conducted the following sensitivity analyses to assess the robustness of the findings: (1) altering the location of knots; (2) excluding studies with flexible dosages; and (3) adjusting the fitting model when necessary.

Results

Search results

The initial search yielded a total of 1,435 records. From the database, we identified 1,414 records, supplemented by 21 references retrieved through manual searches. Two reviewers independently conducted literature screening, resulting in a total of 23 articles included in the systematic review,[14–16,30–49] with 16 articles included in

the DRMA.[14–16,30–35,37–40,42,46] The PRISMA flow diagram illustrates the reasons for exclusion (shown in Fig. 1).

Main characteristics of included studies

The 23 included studies involved 10,351 participants, with 2,512 receiving placebo, 5,689 undergoing vortioxetine treatment, 1,684 prescribed SNRIs (venlafaxine, duloxetine, desvenlafaxine), 220 administered SSRIs (sertraline, escitalopram, paroxetine), and 246 receiving agomelatine treatment. The duration of the experiments ranged from 6 to 8 weeks. Among these studies, two included subjects who exhibited inadequate response to SSRI or SNRI monotherapy for 6 weeks, while the remaining studies did not have this requirement. Ten studies had three arms, six studies had four arms, six had two arms and one had five arms. Seventeen studies employed fixed-dose vortioxetine, while six studies used flexible dosing. It should be noted that in the dose-outcome relationship meta-analysis, we only included studies that contained both vortioxetine and placebo treatment groups. Consequently, only 16 studies comprising 47 treatment groups were included in the DRMA. In the 16 studies analyzed, 2512 participants were allocated to the placebo group, while 4746 were allocated to the vortioxetine group. Specifically, within the vortioxetine group, doses ranged from 1 to 20 mg, with an additional 198 participants receiving flexible doses of 10–20 mg. Detailed information regarding the studies is provided in Table 1.

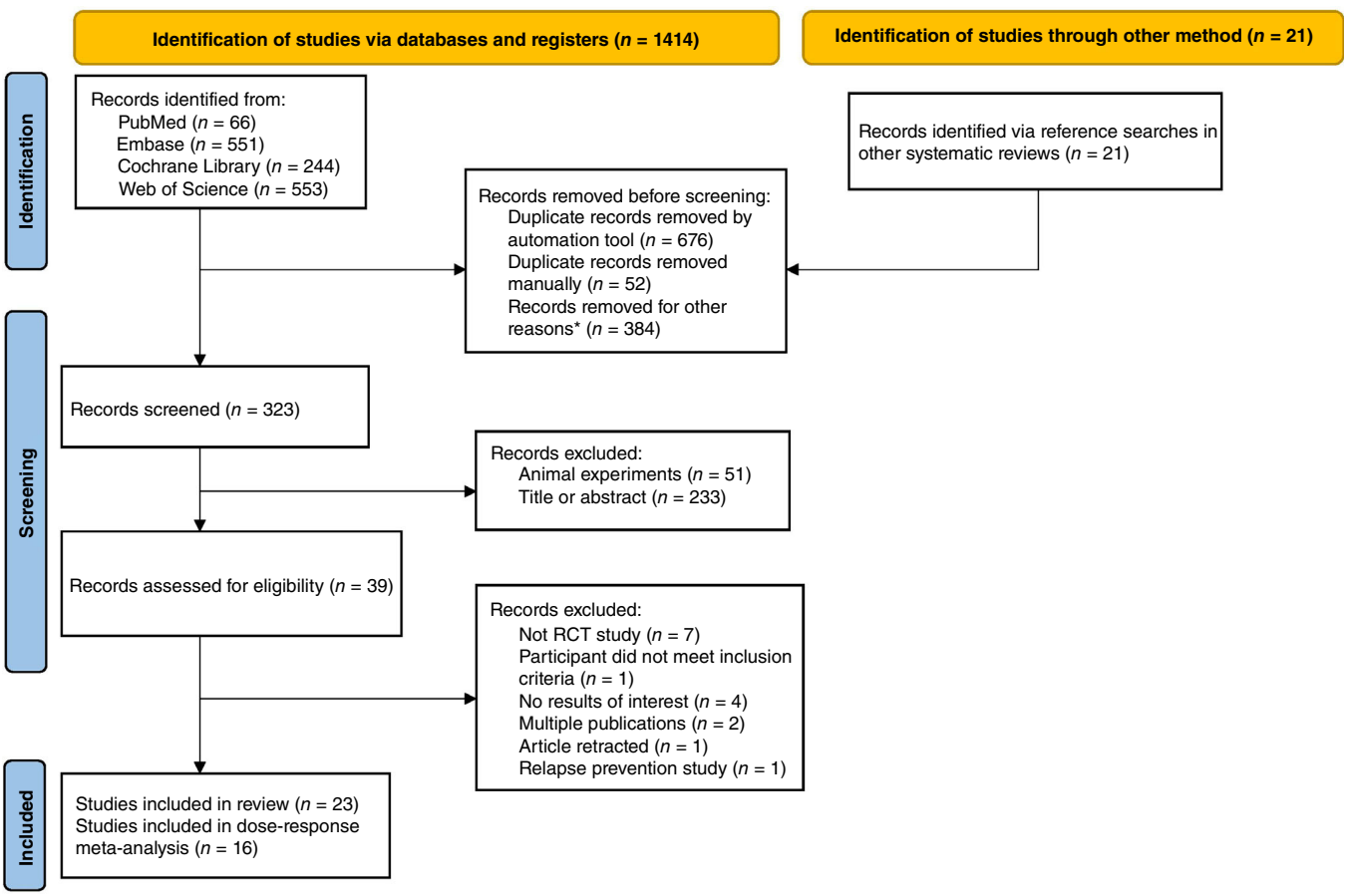
Risk of bias

Detailed information on bias risk assessment is provided in Fig. S1. All studies were rated as having unclear risk of bias in the domain of selective reporting, as detailed study protocols were not disclosed. The majority of studies were also rated as having unclear risk of bias in the domain of other bias, primarily due to being sponsored by pharmaceutical companies (Lundbeck, Takeda) that manufactures vortioxetine. Two studies were rated as high risk in the domain of blinding of participants and personnel, as they were rater-blinded clinical trials. Overall, 11 studies were classified as having low risk, 10 as moderate, and two as high.

Results of the meta-analysis

Efficacy of vortioxetine in MDD

A total of 16 studies comprising 4,294 vortioxetine-treated patients and 2,299 placebo-treated patients were included in the meta-analysis. The results demonstrated that vortioxetine has a small to moderate effect on improving depressive symptoms (Cohen's d = −0.34, 95% CI: −0.43 ∼ −0.26, $I^2 = 59.26\%$, $P < 0.01$), with moderate heterogeneity (shown in Fig. 2). Furthermore, our meta-analysis on response rates revealed that the vortioxetine group had a significantly higher response rate than placebo (RR = 1.37, 95% CI: 1.27 ∼ 1.48, $I^2 = 53.67\%$, $P < 0.01$) (Fig. S2). There is no evidence to suggest a difference in the efficacy of vortioxetine compared to SSRIs in improving depressive symptoms (Cohen's d = 0.02, 95% CI: −0.17 to 0.22, $I^2 = 0\%$, $P = 0.81$) (Fig. S3). When compared to SNRIs, vortioxetine demonstrated inferior efficacy in alleviating depressive symptoms in patients with MDD (Cohen's d = 0.14, 95% CI: 0.06–0.22, $I^2 = 26.46\%$, $P < 0.01$) (Fig. S4).



*Other reasons: meta-analysis, review, case report, trial protocol, conference abstract, editorial material and other types of work.

Fig. 1 Prisma flow-chart of study selection process.

Table 1. Characteristics of the included studies

Study	Study type	Object	Randomized sample size	Age (M ± SD)	Gender (% female)	Race (% white)	Intervention/control	Scale	Study period (weeks)
Alvarez et al., 2012	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS≥30	429	43.3 (11.5)	269 (63%)	392 (92%)	Vortioxetine (5 mg); Vortioxetine (10 mg); venlafaxine (225 mg)/Placebo	MADRS	6
Baldwin et al., 2012	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS≥26	776	Range 18–75	Approximately two-thirds	78%	Vortioxetine (2.5 mg); Vortioxetine (5 mg); Vortioxetine (10 mg); Duloxetine (60 mg)/Placebo	MADRS	8
Henigsberg et al., 2012	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS≥26	560	46.5 (12.2)	351 (63%)	483 (86%)	Vortioxetine (1 mg); Vortioxetine (5 mg); Vortioxetine (10 mg)/Placebo	HAMD-24	8
Katona et al., 2012	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 26, MMSE ≥ 24	452	70.6 (4.9)	297 (66%)	428 (95%)	Vortioxetine (5 mg); Duloxetine (60 mg)/Placebo	HAMD-24; DSST	8
Jain et al., 2013	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 30	600	42.5 (12.8)	350 (58%)	425 (71%)	Vortioxetine (5 mg)/Placebo	HAMD-24	6
Mahableshwarkar et al., 2013	RCT Fixed dose	MDD DSM-IV diagnosed, MADRS≥22	611	42.7 (13.7)	388 (64%)	452 (74%)	Vortioxetine (2.5 mg); Vortioxetine (5 mg); Duloxetine (60 mg)/Placebo	HAMD-24	8
Boulenger et al., 2014	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 26	608	46.7 (13.7)	400 (66%)	596 (98%)	Vortioxetine (15 mg); Vortioxetine (20 mg); Duloxetine (60 mg)/Placebo	MADRS	8
McIntyre et al., 2014	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 26	602	45.7 (12.0)	396 (66%)	95%	Vortioxetine (10 mg); Vortioxetine (20 mg)/Placebo	MADRS; DSST	8
Montgomery et al., 2014	RCT Flexible dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 22, with inadequate response to SSRI or SNRI monotherapy	501	46.5 (12.0)	370 (75%)	Almost 100%	Vortioxetine (10–20 mg)/Agomelatine (25–50 mg)	MADRS	8
Jacobsen et al., 2015	RCT Fixed dose	MDD DSM-IV, SCID diagnosed, MADRS ≥ 26	462	42.8 (12.2)	335 (73%)	323 (70%)	Vortioxetine (10 mg); Vortioxetine (20 mg)/Placebo	MADRS	8
Mahableshwarkar et al., 2015a	RCT Fixed dose	MDD DSM-IV diagnosed, MADRS ≥ 26	614	42.9 (12.3)	453 (74%)	470 (77%)	Vortioxetine (15 mg); Vortioxetine (20 mg); Duloxetine (60 mg)/Placebo	MADRS	8
Mahableshwarkar et al., 2015b	RCT Fixed dose	MDD DSM-IV, SCID diagnosed, MADRS≥26	469	45.1 (12.4)	329 (70%)	348 (74%)	Vortioxetine (10 mg); Vortioxetine (15 mg)/Placebo	MADRS	8
Mahableshwarkar et al., 2015c	RCT Flexible dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 26	602	45 (11.9)	392 (65%)	516 (86%)	Vortioxetine (10–20 mg); Duloxetine (60 mg)/Placebo	MADRS; DSST	8
Wang et al., 2015	RCT Fixed dose	MDD DSM-IV, MINI diagnosed, MADRS ≥ 26	443	40.5 (12.0)	262 (60%)	Asian 100%	Vortioxetine (10 mg)/Venlafaxine (150 mg)	MADRS	8

Table 1. (*Continued*)

Study	Study type	Object	Randomized sample size	Age (M ± SD)	Gender (% female)	Race (% white)	Intervention/control	Scale	Study period (weeks)
Baune et al., 2018	RCT Fixed dose	MDD DSM-IV diagnosed, MADRS ≥ 26	152	46.2 (12.0)	100 (67%)	148 (99%)	Vortioxetine (10 mg); Paroxetine (20 mg)/placebo	MADRS; DSST	8
Inoue et al., 2018	RCT Fixed dose	MDD DSM-IV diagnosed, MADRS≥26	366	38.4 (10.8)	171 (47%)	Not reported	Vortioxetine (5 mg); Vortioxetine (10 mg)/Placebo	MADRS	8
Nishimura et al., 2018	RCT Fixed dose	MDD DSM-IV diagnosed, MADRS ≥ 26	600	44.4 (11.5)	375 (63%)	414 (69%)	Vortioxetine (5 mg) Vortioxetine (10 mg) Vortioxetine (20 mg)/Placebo	MADRS	8
Vieta et al., 2018	RCT Flexible dose	MDD DSM-IV diagnosed, MADRS ≥ 22, PHQ-9 ≥ 14, PDQ-D ≥ 25, with inadequate response to SSRI or SNRI monotherapy	101	48.2 (10.6)	74 (75%)	100%	Vortioxetine (10–20 mg)/Escitalopram (10–20 mg)	PHQ-9; DSST	8
Borhannejad et al., 2020	RCT Fixed dose	MDD DSM-5, SCID diagnosed, HAMD-17 ≥ 19	60	70.6 (8.2)	37 (74%)	Not reported	Vortioxetine (15 mg)/ Sertraline (75 mg)	HAMD-17	6
Inoue et al., 2020	RCT Fixed dose	MDD DSM-IV diagnosed; MADRS≥26	493	40.0 (10.8)	224 (45%)	Not reported	Vortioxetine (10 mg); Vortioxetine (20 mg)/Placebo	MADRS	8
Lee et al., 2022	RCT Rater-Blinded Flexible	MDD DSM-5 diagnosed, HAMD-17 ≥ 14	121	38.1 (14.4)	69 (57%)	Not reported	Vortioxetine (10–20 mg)/ Escitalopram (10–20 mg)/ Desvenlafaxine (50–200 mg)	HAMD-17; MADRS	6
Mclntyre et al., 2023	RCT Flexible dose	MDD DSM-5, MINI diagnosed, MADRS≥24; partial response to SSRI monotherapy	605	43.2 (12.8)	427 (71%)	92%	Vortioxetine (10–20 mg)/ Desvenlafaxine (50 mg)	MADRS	8
Shin et al., 2023	RCT Rater-Blinded Flexible	MDD DSM-5 diagnosed; HAMD-17 ≥ 14; HAMA ≥ 14	124	41.4 (16.1)	96 (77%)	Not reported	Vortioxetine (10–20 mg)/ Escitalopram (10–20 mg)/ Desvenlafaxine (50–200 mg)	HAMD-17	6

DSM, diagnostic and statistical manual of mental disorders; DSST, digit symbol substitution test; HAM-D, Hamilton depression rating scale; MADRS, Montgomery-Åsberg depression rating scale; MDD, major depressive disorder; PDQ-D, perceived deficits questionnaire-depression; PHQ-9, patient health questionnaire-9; RCT, randomized controlled trial; SCID, structured clinical interview for DSM disorders; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Dropout rate for any reason (acceptability)

Fifteen studies involving 6,754 participants provided data on dropout rates due to any reasons. The meta-analysis results indicate that the vortioxetine group exhibits a slightly higher overall dropout rate compared to the placebo group (RR = 1.11, 95% CI: 1.00 ∼ 1.23, $I^2 = 7.98\%$, $P = 0.04$) (Fig. S5). This suggests a potential increased risk of treatment discontinuation among individuals receiving vortioxetine relative to placebo recipients. However, further investigation is warranted to fully elucidate the clinical significance of this disparity.

Dropout rate for adverse events (tolerability)

Sixteen studies provided data on dropout rate due to adverse events. Evidence suggests that participants receiving vortioxetine treatment had a greater number of dropout due to adverse events compared to the placebo group (RR = 1.39, 95% CI: 1.15–1.69, $I^2 = 0\%$, $P < 0.01$) (Fig. S6).

Adverse events (safety)

Data from 16 studies was analyzed to assess the rate of adverse events. Evidence suggests that the rate of adverse events in the vortioxetine group is slightly higher than that in the placebo group (RR = 1.11, 95% CI: 1.07 ∼ 1.14, $I^2 = 4.13\%$, $P < 0.01$) (Fig. S7).

Results of subgroup analysis

We conducted subgroup analyses based on different doses for efficacy, dropout for any reasons, dropout due to adverse events, and

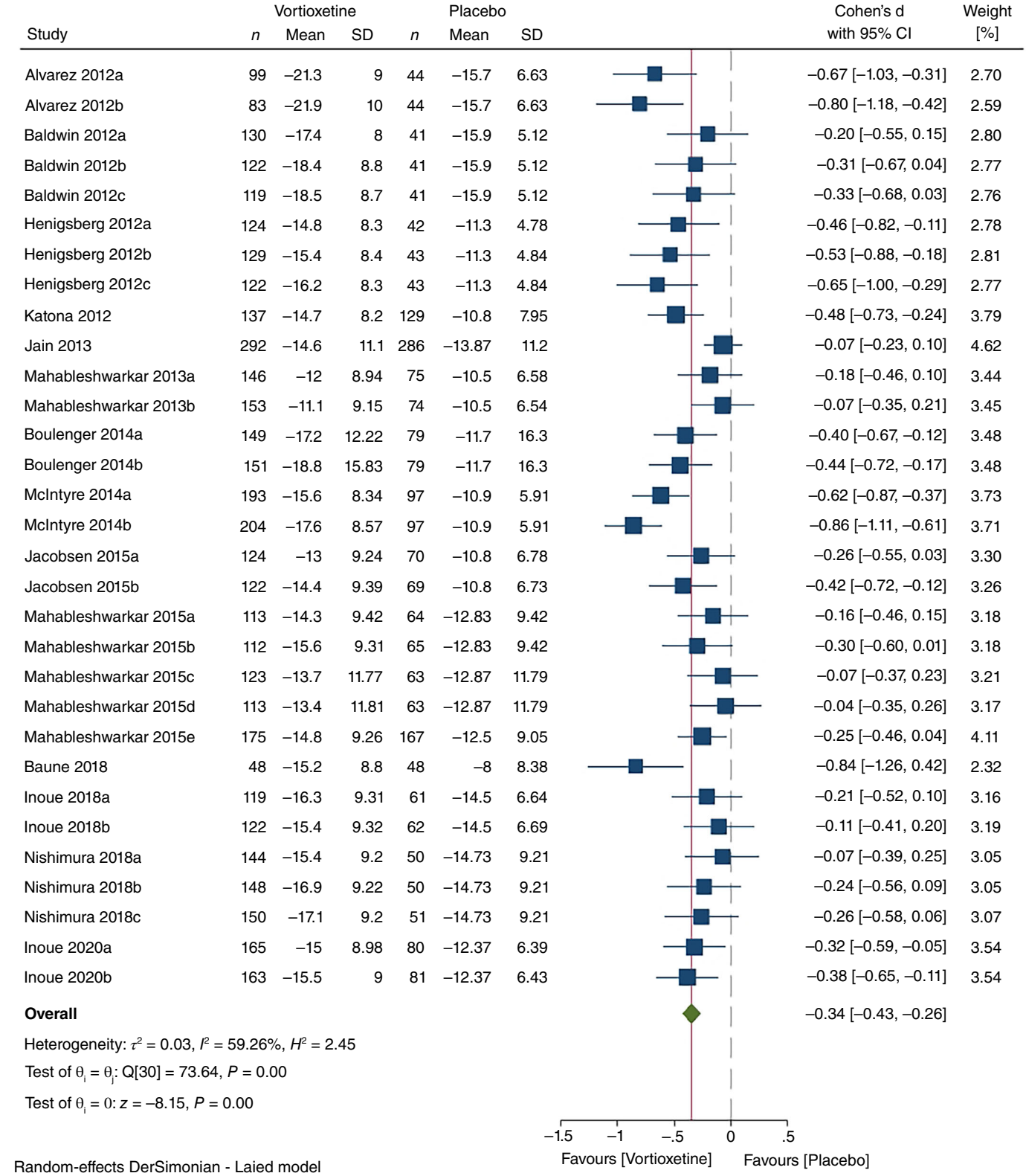


Fig. 2 Meta-analysis of vortioxetine versus placebo: Mean change in depression symptom scores.

adverse events (Figs S8–S12). Although lower dose groups generally showed smaller effect sizes compared to higher dose groups, there were no significant differences observed among the dose groups (Test of group differences: $P \geq 0.05$).

Dose-outcome relationships for vortioxetine

The dose–response curves for vortioxetine in efficacy, dropout due to any reasons, dropout due to adverse events, and adverse events are depicted in Figs 3 and 4. Visual inspection of the dose–response

curve showed that efficacy increased linearly as the dose escalated from 0 to 5 mg/day, slowed between 5 and 10 mg/day, and then continued to rise linearly from 10 to 20 mg/day (Fig. 3a), without reaching a plateau at 20 mg/day. The estimated ED50 was 4.37 mg/day (95% CI: 2.76–7.61), and the ED95 was 17.93 mg/day (95% CI: 7.91–18.75). The dose–response curve for response resembles the trend observed for SMD (Fig. 3b). The maximum RR of 1.40 (95% CI: 1.21–1.63) was observed at 20 mg/day.

After fitting the data using a one-stage restricted cubic spline model, we observed non-significant coefficients for dropout due to any reasons ($\beta1 = 0.0122$, $P = 0.19$; $\beta2 = -0.0110$, $P = 0.63$) with an Akaike information criterion (AIC) of 34.98, and for dropout due to adverse events ($\beta1 = 0.0515$, $P = 0.17$; $\beta2 = -0.0193$, $P = 0.57$) with an AIC of 60.57, indicating poor model fit. Therefore, a two-stage linear model was employed for dose–response estimation for both outcomes. The RR for dropout due to any reasons, dropout due to adverse events, and adverse events all exhibited an upward trend with increasing doses (Fig. 4). Specifically, the RR for dropout due to any reasons gradually escalated from 1 at placebo (0 mg/day) to 1.22 (95% CI: 1.01–1.48) at 20 mg/day (Fig. 4a). Similarly, the RR for dropout due to adverse events rose from 1 at placebo to 1.98 (95% CI: 1.36–2.87) at 20 mg/day (Fig. 4b). Additionally, the RR for adverse events reaches its peak at 1.18 (95% CI: 1.12–1.25) at 20 mg/day (Fig. 4c).

Sensitivity analyses

The primary meta-analysis results, focusing on changes in depression scores, underwent sensitivity analysis using a leave-one-out method (Fig. S13), revealing the robustness of the meta-analysis findings. Additionally, we conducted a sensitivity analysis for the DRMA. Dose-outcome curves, drawn with varying knots, are provided in Fig. S14. Another set of dose-outcome curves, comprising solely fixed-dose studies, was depicted in Fig. S15. We utilized one-stage restricted cubic spline model, two-stage restricted cubic spline model, and two-stage linear model to fit dose-outcome relationships for dropout due to any reasons and dropout due to adverse events (Fig. S16). It is noteworthy that when we characterized the dose–response relationship using knots located at the 30th, 60th, and 90th percentiles, we observed a plateau in the curve at higher doses. The trends observed in other curves were similar to our initial findings.

Publication bias

We assessed publication bias using funnel plots and Egger's regression test. The roughly symmetric distribution of data points in the funnel plot may suggest the absence of publication bias (Fig. S17), further confirmed by Egger's regression test ($P = 0.11$).

Discussion

In our meta-analysis, encompassing 16 randomized controlled trials with a total of 6,593 participants, vortioxetine demonstrated small to moderate effects in alleviating depressive symptoms compared to placebo, confirming findings from previous clinical trials and meta-analyses.[7,50,51] This underscores the clinical significance of vortioxetine as a viable treatment option for patients with severe depression. However, it is noteworthy that while statistically significant, observed effect sizes may have limited clinical significance in some cases, especially when considering individual patient responses and the broader range of available antidepressants (e.g., SSRIs, SNRIs).[47,49] As our study results indicate, vortioxetine showed no statistically significant difference in alleviating depressive symptoms compared to SSRIs, while SNRIs were superior to vortioxetine in this regard. It should be noted that subgroup analysis of SNRIs revealed no significant difference in efficacy compared to venlafaxine (Cohen's $d = 0.03$, 95% CI: −0.20–0.25, $I^2 = 44.8\%$) and desvenlafaxine (Cohen's $d = 0.23$, 95% CI: −0.17–0.63, $I^2 = 75.6\%$) (Fig. S18). However, vortioxetine exhibited slightly inferior efficacy compared to duloxetine (Cohen's $d = 0.19$, 95% CI: 0.10–0.27, $I^2 = 0\%$) (Fig. S18), consistent with previous research findings.[52] Regarding acceptability, our study findings suggest that vortioxetine treatment was associated with a slightly higher all-cause dropout rate compared to placebo, which is inconsistent with previously published meta-analysis results.[50] The disparity in study findings may be attributed to the inclusion of more studies, thus synthesizing a broader evidence base. However, it is important to note that our results are on the borderline of significance (RR = 1.11, 95% CI: 1.00–1.23, $I^2 = 7.98\%$, $P = 0.04$), necessitating cautious interpretation and further confirmation through additional research. Additionally, we found that vortioxetine had lower tolerability and safety compared to placebo, emphasizing the importance of vigilance and monitoring for adverse reactions, especially at higher doses where tolerability and safety may be compromised. Subgroup analysis based on different dosage revealed no significant differences in acceptability, tolerability, and safety among the dosage groups. These findings may indicate that despite vortioxetine demonstrating lower acceptability, tolerability, and safety compared to placebo, escalating the dosage did not significantly decrease the drug's acceptability, tolerability, and safety. Nonetheless,

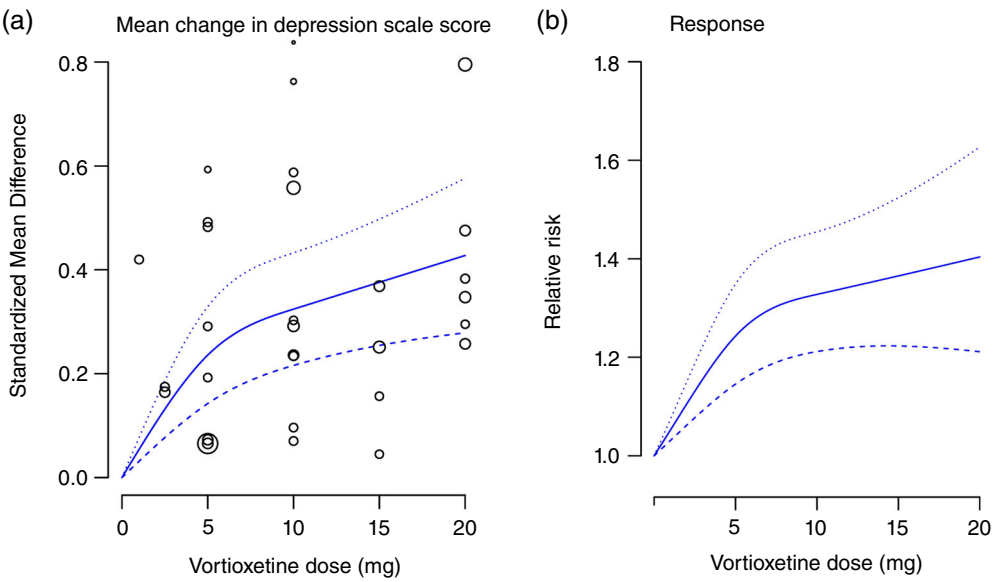


Fig. 3 Dose–response curves for efficacy of vortioxetine estimated using a one-stage restricted cubic spline model. Dash lines represent the 95% confidence intervals for the spline mode. (a) The curve represents the standardized mean differences reduction of depressive symptoms for the vortioxetine treatment groups compared to the placebo groups (solid line), $n = 16$, $N = 6593$. The estimated dose to produce 50% (ED50) of the predicted maximum effect was reached for the dose of 4.37 mg (95% CI: 2.76–7.61). ED95 was 17.93 mg (95% CI: 7.91–18.75). Circles indicate observed standardized mean differences in individual studies; size of each circle is proportional to precision (inverse of variance) of the standardized mean differences. (b) The curve represents the dose–response relationship between vortioxetine dose and response rate (solid line). The relative risk is plotted on the log scale using the placebo group (0mg/day) as the reference. ED50 was estimated at 3.59 (95% CI: 2.44–7.01); ED95 was 16.96mg (95% CI: 5.98–18.68).

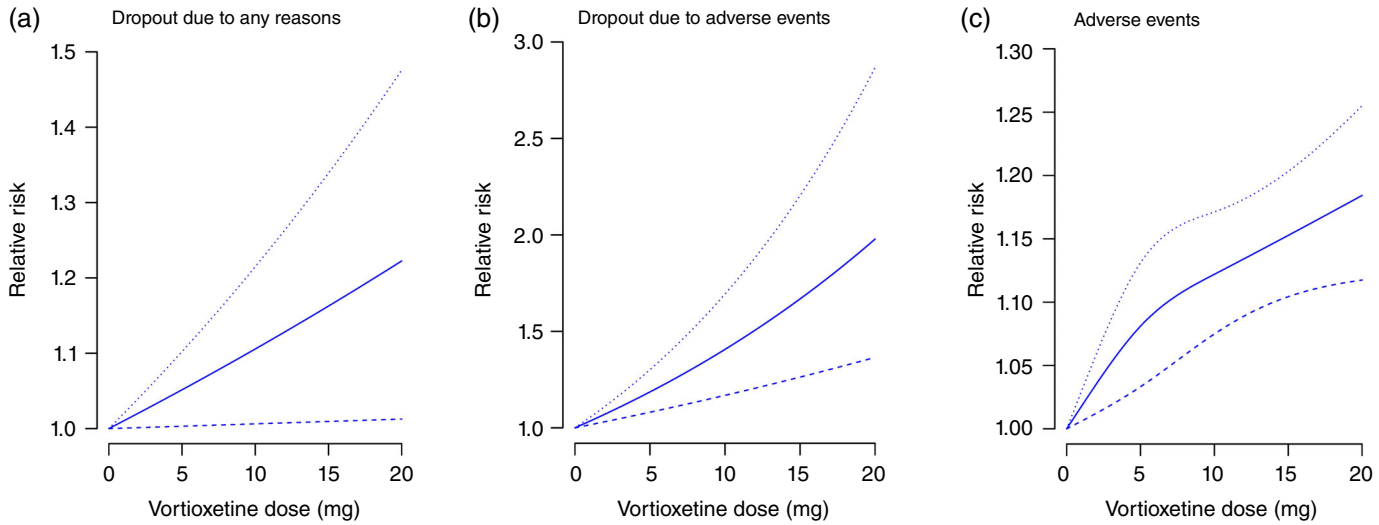


Fig. 4 Dose-outcome relationships for vortioxetine. Dash lines represent the 95% confidence intervals. (a) and (b) were estimated using a two-stage linear model (solid line). (c) was estimated using a one-stage restricted cubic spline model (solid line).

additional head-to-head studies involving diverse dosage groups are required to confirm these findings.

Furthermore, our analysis indicates a potential dose-dependent effect of vortioxetine on depression, consistent with prior research findings.[51,53] Within the range examined, higher doses were associated with greater efficacy but also higher rates of adverse events, all-cause dropout, and dropout due to adverse events. In the dose–response curve depicting the effect of vortioxetine on alleviating depressive symptoms (Fig. 3a), we noted a linear increase in efficacy as the dose ranged from 0 to 5 mg/day. This trend slowed between 5 and 10 mg/day, followed by a gradual linear rise from 10 to 20 mg/day, without reaching a plateau. At the maximum dose of 20 mg/day, compared to placebo (0 mg/day), the relative risk of dropout for any reasons increased by 1.22 times, adverse events increased by 1.18 times, and the risk of dropout for adverse events increased by 1.98 times. Despite observing an upward trend, subgroup analyses indicated no significant differences among dosage groups. Previous dose–response meta-analyses found that SSRIs, venlafaxine, and mirtazapine achieved the optimal balance of efficacy, acceptability, and tolerability at the lower range of the licensed dose.[54] Our study suggested that vortioxetine may potentially provide increased efficacy beyond the current maximum licensed dosage without significant effects on its acceptability, tolerability, and safety. Vortioxetine appears to remain safe and effective at higher doses, which is different from SSRIs, venlafaxine, and mirtazapine. In the future, we still need more randomized controlled trials of vortioxetine at doses exceeding 20mg/day to provide evidence for the efficacy and risk relationship of vortioxetine at high doses.

It is important to note that we observed three studies[38–40] at the 15 mg/day dose with SMD values significantly lower than the SMD value at 15 mg/day on the dose-efficacy curve. The possible reasons for this are: (1) Compared to the 5, 10, and 20 mg/day groups, the 15 mg/day group has a smaller sample size, and the observed results may not accurately reflect the efficacy of vortioxetine; (2) The studies with lower effect sizes were conducted in the United States (US). There might be heterogeneity between studies conducted in different regions, resulting in varying efficacy of vortioxetine. Previous meta-analyses have indicated that the efficacy of vortioxetine for MDD is lower in the US compared to non-US.[51] The impact of region on vortioxetine efficacy can be referenced from the study by Thase et al.[51] Although our dose–response curve shows local inconsistencies with the current evidence, it is overall consistent with the existing evidence. More randomized controlled trials of vortioxetine at 15 mg/day are needed in the future to validate our findings.

Our study has several limitations. Firstly, participants included in the DRMA were all patients with MDD, excluding those with treatment-resistant depression and patients with MDD comorbid with anxiety disorders. Therefore, caution is needed when extrapolating the results to other MDD subgroups (e.g., first-episode MDD, elderly MDD). Secondly, the majority of studies we included employed fixed-dose study designs. While fixed-dose studies are essential for rigorously examining dose-dependency, they may overestimate dropout rates due to adverse reactions, particularly in some high-dose studies. Thirdly, we included studies with flexible dosing. It's worth noting that, because flexible dosing studies do not specify exact doses, dose determination relies on assumptions, which may influence the results. Although we addressed this limitation in sensitivity analyses, the interpretation of curve trends relied solely on visual inspection. Fourth, in our sensitivity analysis, we observed that setting the knots for the restricted cubic spline model at the 25th, 50th, and 75th percentiles resulted in a plateau in the curve of response at high doses (Fig. S14). This diverges from our initial findings, suggesting that the dose–response curve may be significantly influenced by the chosen knot. Caution is warranted in interpreting our results due to this potential variability. Finally, the studies included in the meta-analysis were all sponsored by vortioxetine drug manufacturers, which may introduce potential conflicts of interest, potentially impacting the experimental outcomes and leading to errors in our research conclusions.

Conclusions

Our study provides increasing evidence regarding the efficacy, acceptability, tolerability, and safety of vortioxetine in treating MDD. Our findings indicate that vortioxetine may be more effective than placebo but inferior in acceptability, tolerability and safety. We found dose–response relationships of vortioxetine for MDD, with efficacy increasing with dose while acceptability, tolerability, and safety decrease. Exceeding the current approved dosage may potentially provide additional therapeutic benefits without significantly impacting safety. More studies, particularly exceeding approved doses, are needed to identify the most effective dosing pattern in terms of efficacy and risk.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

XY and SF: conceptualization, data curation, formal analysis, methodology, validation, software, visualization, writing – original draft and writing – review and editing; WL, YH, HX, XJ, YurZ, YuwZ and JL: data curation, methodology, validation and writing – original draft; WK: conceptualization, formal analysis, methodology, visualization, resources, supervision, funding acquisition and writing – review and editing. All authors read and approved the final manuscript.

Data availability statement

All the data of the current study are available upon reasonable request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section at the end of this article.