

Evaluation of the efficacy and safety of vilazodone for treating major depressive disorder

Xiao-Fei Zhang
Lei Wu
Dong-Jun Wan
Ruo-Zhuo Liu
Zhao Dong
Min Chen
Sheng-Yuan Yu

Department of Neurology, Chinese
PLA General Hospital, Beijing,
People's Republic of China

Purpose: Vilazodone is a novel serotonin (5-HT)-reuptake inhibitor and 5-HT_{1A} partial agonist that was recently developed for the treatment of major depressive disorder (MDD). We conducted a meta-analysis and systematic review to better evaluate the efficacy and safety of vilazodone.

Materials and methods: We performed a thorough literature search to identify all randomized double-blind placebo-controlled trials that were designed to investigate the efficacy of vilazodone for the treatment of MDD, and that were published in electronic databases, including Medline, Embase, and the Cochrane Central Register of Controlled Trials. A manual search was also conducted to investigate the relevant references of the retrieved studies. Subsequently, we conducted a meta-analysis and systematic literature review.

Results: A total of five randomized controlled trials were finally included, involving 1,200 patients with vilazodone and 1,193 patients with placebo. The primary efficacy end point of the Montgomery-Åsberg Depression Rating Scale (standardized mean difference -3.58 , 95% confidence interval -4.59 to -2.56 ; $P < 0.00001$), and the key secondary efficacy end points (Clinical Global Impression - Severity scale, Clinical Global Impression - Improvement scale, and Hamilton Anxiety Rating Scale) indicated that vilazodone was more effective than placebo. Most common adverse events, including diarrhea and nausea, were evaluated, and safety assessments indicated that vilazodone was well tolerated (diarrhea odds ratio 3.54, 95% confidence interval 2.81–4.45; $P < 0.00001$; nausea odds ratio 3.85, 95% confidence interval 3.00–4.96; $P < 0.00001$; discontinuations due to adverse events odds ratio 2.71, 95% confidence interval 1.81–4.05; $P < 0.00001$).

Conclusion: Our findings indicate that the novel antidepressant vilazodone is effective and safe for MDD, with a low occurrence of side effects. It offers promise as an effective oral drug for the treatment of MDD, with a balance of efficacy and tolerability.

Keywords: vilazodone, major depression, systematic review, antidepressant, randomized controlled trial

Introduction

Major depressive disorder (MDD) is a serious chronic and recurrent psychiatric illness, and accounts for 10%–14% of all patients seen by primary care physicians.^{1–3} It is the third major cause of moderate-to-severe disability and worldwide burden of disease.^{4,5} The cardinal symptoms of MDD include diminished pleasure or interest in daily activities, changes in appetite or weight, sleep disorders, difficulty concentrating, fatigue, psychomotor agitation, sad mood, feelings of worthlessness, and even suicidal thoughts.⁶ Despite the current availability of different types of antidepressants, many patients with depression do not achieve adequate remission after treatment. Selective serotonin (5-HT)-reuptake inhibitors (SSRIs) are relatively effective treatments for MDD and the most commonly prescribed first-line treatment options. Many patients

Correspondence: Sheng-Yuan Yu
Department of Neurology, Chinese
PLA General Hospital, 28 Fuxing Road,
Haidan District, Beijing 100853, People's
Republic of China
Tel/fax +86 10 68182255
Email yusy1963@126.com

may show strong response to or tolerate a different SSRI⁷ if they do not adequately respond to or do not tolerate their initial SSRI.⁸ Although all SSRIs modulate serotonin reuptake, they differ in their pharmacologic profiles, which may influence efficacy and tolerability in individual patients. It is necessary to explore novel medications with superior clinical efficacy and good tolerability for patients with MDD.

Vilazodone is a new antidepressant with a unique mechanism of action whereby it simultaneously acts as an SSRI and a 5-HT_{1A}-receptor partial agonist.⁹⁻¹² It was approved in 2011 by the US Food and Drug Administration for the treatment of MDD in adults.¹³ Clinicians have speculated that because vilazodone combines serotonin-reuptake inhibition and has a buspirone-like anxiolytic mechanism, it could be an effective and well-tolerated class of drug for patients with MDD symptoms.^{14,15}

The purpose of the present study was to review the currently available clinical studies referring to vilazodone and to summarize all the data to objectively evaluate the efficacy of this antidepressant for the treatment of MDD by meta-analysis.

Materials and methods

Data sources and search strategy

All randomized controlled trials (RCTs) reporting the effect of vilazodone for treating MDD were systematically searched in the Medline, Embase, and Cochrane Central Register of Controlled Trials databases until April 2015. In our search strategy, the following keywords were used: “vilazodone”,

“major depressive disorder”, and “randomized controlled trial”. In addition, a manual search was conducted to investigate the relevant references of the retrieved publications.

Inclusion criteria

All the selected articles were screened according to the following criteria for inclusion: 1) articles referring to treatment with vilazodone for patients with MDD, 2) detailed data including the values of each index and the total number of each group available to be analyzed, 3) published as a full text up to April 2015. If the same author reported various articles sharing the identical case series, only the study with the most patients was used, and if the same research was published in different journals, only the most recent article was included for analysis. The flowchart depicting the study-selection process is presented in Figure 1.

Quality assessment

We assessed the methodological quality of each trial using the Jadad scale¹⁶ according to the following aspects: how the participants were allocated to the group of the studies, whether the articles stated explicitly the method of blinding, and whether they described the missing data due to attrition and explained the reason for dropouts. Based on the guidelines published in the *Cochrane Handbook for Systematic Reviews of Interventions*,¹⁷ each trial was then classified qualitatively and assigned to one of the three following rates: A, if the study met all quality criteria adequately and a low risk of bias was thought to exist; B,

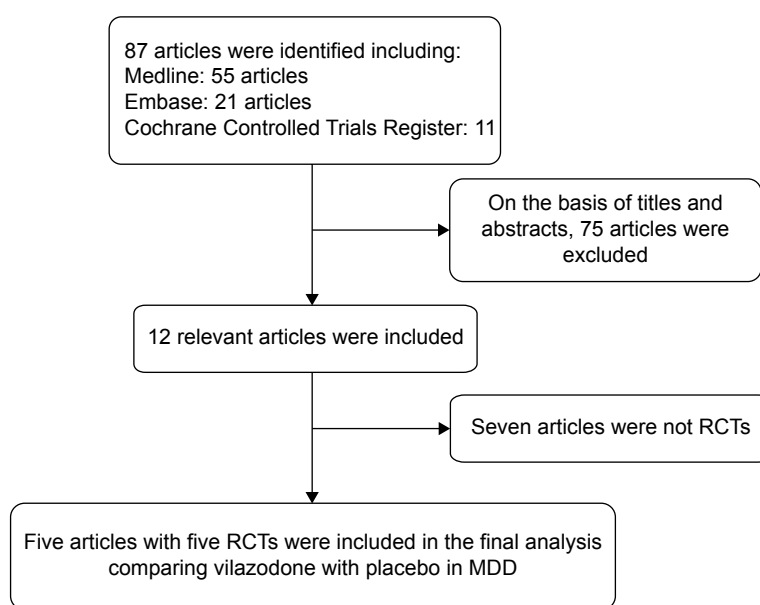


Figure 1 Flow diagram of the study-selection process.

Abbreviations: RCTs, randomized controlled trials; MDD, major depressive disorder.

if the study partially met one or more of the quality criteria or the criteria were unclear and a moderate risk of bias was thought to exist; and C, if the study did not meet or include one or more of the criteria and a high risk of bias was thought to exist.

Data extraction

Usable information was collected from each paper: 1) first author's name, 2) sample size, 3) country of the study, 4) year of publication, 5) therapy that the persons were treated with, and 6) data including the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression - Severity scale (CGI-S), CGI - Improvement scale (CGI-I), Hamilton Anxiety Rating Scale (HAMA), diarrhea, nausea, and discontinuations due to an adverse event (AE).

Statistical analysis

Relevant data included in the meta-analysis were compared by using RevMan version 5.1.0.¹⁷ Differences between entry and completion of study were evaluated according to changes in MADRS, CGI-S, CGI-I, HAMA, diarrhea, nausea, and discontinuations due to an AE. We used the fixed-effect model (Mantel-Haenszel method) and random-effect model (DerSimonian-Laird method) to evaluate the standardized mean difference for continuous data and the relative risk for dichotomous results pooled across studies with a corresponding 95% confidence interval (CI).¹⁸ The study was considered to be homogeneous only when the analysis showed $P > 0.05$, and then the fixed-effect model was chosen for meta-analysis; otherwise, the random-effect model was considered more appropriate. Inconsistency across studies was quantified by the I^2 statistic, which describes the true extent of heterogeneity but not as a result of chance in results.¹⁹ I^2 values ranged from 0% to 100%, representing a low level of heterogeneity if $I^2 < 25%$ and significant inconsistency if $I^2 > 50%$.

Results

Characteristics of included studies

Initially, a total of 87 articles that may have offered usable data for our meta-analysis were included by the electronic and manual searches. We removed 75 studies after reviewing the titles and abstracts of the included articles according to the predefined inclusion and exclusion criteria. Among the remaining 12 articles, seven articles were excluded as not RCTs, and thus five RCTs²⁰⁻²⁴ that compared vilazodone with placebo were considered eligible for the analysis (Figure 1). The relevant information about the five included articles is listed in Table 1.

Table 1 Study and patient characteristics

Study	Therapy in experimental group	Therapy in control group	Country	Sample size		Administration method	Duration of treatment	Dosage	Inclusion population
				Experimental	Control				
Rickels et al ²⁰	Vilazodone	Placebo	US	205	205	Oral	8 weeks	40 mg/day	Adults with MDD who had an ongoing major depressive episode lasting ≥ 4 weeks and ≤ 2 years, and had an HDRS-17 total score ≥ 22 and an HDRS-17 item single score ≥ 2
Khan et al ²¹	Vilazodone	Placebo	US	231	232	Oral	8 weeks	40 mg/day	Adults with MDD who had an ongoing major depressive episode lasting ≥ 4 weeks and ≤ 2 years, and had an HDRS-17 total score ≥ 22
Croft et al ²²	Vilazodone	Placebo	US	253	252	Oral	8 weeks	40 mg/day	Adults with MDD who had an ongoing major depressive episode lasting ≥ 8 weeks and up to 12 months, and had an MADRS total score ≥ 26
Mathews et al ²³	Vilazodone	Placebo	US	284	281	Oral	8 weeks	40 mg/day	Adults with MDD who had an ongoing major depressive episode lasting ≥ 8 weeks and up to 12 months, and had an MADRS total score ≥ 26
Gommoll et al ²⁴	Vilazodone	Placebo	US	227	223	Oral	10 weeks	40 mg/day	Participants with HAMA total score ≥ 20 , HAMA items 1 and 2 scores ≥ 2 and CGI-S score ≥ 4

Abbreviations: MDD, major depressive disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; CGI-S, Clinical Global Impression - Severity scale.

Quality of each study

All of the studies included were double-blinded RCTs. Each described how to run the randomization processes and confirmed the optimal sample size by power-calculation methodologies (Table 2). The quality level of each study was A (Table 2). A funnel plot was performed through software to analyze whether the studies had statistical evidence of publication bias. It reflected the relationship between treatment effect and sample size for each included study. From the funnel plot, no significant publication bias was found (Figure 2).

Efficacy

To evaluate the efficacy of vilazodone for patients with MDD, we analyzed the data referring to MADRS, CGI-S, CGI-I, and HAMA. As for MADRS, only four of the five studies were included, representing 1,943 patients (973 in the vilazodone group and 970 for placebo), and the remaining indices were all studied in the five articles, which included 2,393 patients (1,200 in the vilazodone group and 1,193 in the placebo group) (Figure 3). After the analysis, we got similar results for the indexes (MADRS, CGI-S, CGI-I, and HAMA): no significant heterogeneity was detected across studies ($P > 0.05$ for all), and the fixed-effect model was then performed. As shown in Figure 3, the pooled estimates for standardized mean difference were -3.58 , -0.33 , -0.54 , and -1.64 (95% CI -4.59 to -2.56 , -0.41 to -0.25 , -0.62 to -0.46 , and -2.07 to -1.22 , respectively; $P < 0.00001$ for all). Based on the meta-analysis, it was proven that compared with placebo, vilazodone showed dramatically greater reductions in MADRS, CGI-S, CGI-I, and HAMA scores.

Safety

As for the common AEs with vilazodone, diarrhea, nausea, and discontinuation due to AE data were evaluated in the five studies, including 2,393 participants (1,200 in the vilazodone group and 1,193 in the placebo group) (Figure 4). In the subsequent analysis, effect size was expressed as odds ratios (ORs). Compared with the control group, five RCTs showed diarrhea data (OR 3.54, 95% CI 2.84–4.45; $P < 0.00001$), nausea data (OR 3.85, 95% CI 3.00–4.96; $P < 0.00001$), and discontinuation due to AE data (OR 2.71, 95% CI 1.81–4.05; $P < 0.00001$) (Figure 4). These results suggested that the incidences of diarrhea and nausea in the vilazodone group were higher than in the placebo group, and discontinuation due to AEs was significantly less likely to occur with the placebo.

Table 2 Quality assessment of individual studies

Study	Allocation-sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	ITT analysis	Level of quality
Rickels et al ²⁰	A	A	A	101	Yes	Analysis of covariance	Yes	A
Khan et al ²¹	A	A	A	128	Yes	Analysis of covariance	Yes	A
Croft et al ²²	A	A	A	120	Yes	Analysis of covariance	Yes	A
Mathews et al ²³	A	A	A	62	Yes	Mixed-effect model	Yes	A
Gommoll et al ²⁴	A	A	A	19	Yes	Analysis of covariance	Yes	A

Notes: Quality assessment rated as: A, all quality criteria met (adequate) – low risk of bias; B, one or more of the quality criteria only partly met (unclear) – moderate risk of bias; C, one or more criteria not met (inadequate or not used) – high risk of bias.

Abbreviation: ITT, intention-to-treat.

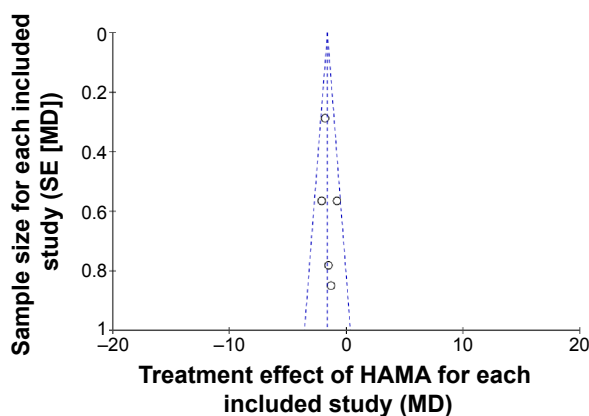


Figure 2 Funnel-plot analysis to detect publication bias.

Notes: Each circle represents the indicated association between treatment effect and sample size for an individual study.

Abbreviations: MD, mean difference; SE, standard error.

Discussion

Depression is the most common psychiatric disorder and a leading cause of disability worldwide.^{25,26} It is reported that an estimated 8 million individuals meet criteria for MDD, and about 10% of the adult population experiences a major depressive episode each year in the US.^{27,28} Changes in cognitive–emotional and physical symptoms of depression translate to extensive impairments in psychosocial functioning across physical, occupational, and social domains that severely affect the patient’s quality of life.^{29,30} The likelihood of long-term treatment success is improved with early, quick, and accurate diagnosis, multidimensional assessment, and rational pharmacotherapy tailored to each patient’s symptomatology, coexisting disorders, and treatment needs.³¹ The first-generation antidepressants are classified as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).³² The side-effect profile of these two drug classes is one of the major factors that limit their use. Compared with MAOIs and TCAs, in general SSRIs have been found to show similar efficacy in the treatment of depressed outpatients, with a better tolerability profile.³³ As a result, TCAs and MAOIs were rapidly supplanted by SSRIs as the first choice for both psychiatrists and primary care providers for treating depression.³⁴

Vilazodone, which is the first of a new class of antidepressants called indolealkylamines, has been approved for the treatment of MDD and has dual-acting properties combining SSRI and 5-HT_{1A} partial agonist activity.¹³ On the basis of its unique action mechanism for patients with depression, vilazodone offers the potential advantage of faster treatment effect with lower AE risks characterized by good tolerability compared with currently used antidepressants.

Several articles reviewing the currently available studies about vilazodone showed that it was an effective and safe treatment option with its novel action mechanisms for patients with depression.^{35–37} We further evaluated similar aims through a meta-analysis, which was thought to be a reliable and objective approach. To our knowledge, this is the first study to conduct a thorough meta-analysis studying the efficacy and safety of vilazodone for treating MDD. Based on the meta-analysis, vilazodone at 40 mg per day proved to be superior to placebo in improving MADRS, CGI-S, CGI-I, and HAMA scores. Our study shows that treatment with vilazodone can offer both statistically significant and more importantly clinically satisfactory improvements for patients with MDD. Three of the RCTs evaluating the 17-item Hamilton Depression Rating Scale (HDRS-17) also showed that vilazodone was superior to placebo in improving the symptoms of MDD.^{20,21,24} Among these, Rickels et al²⁰ analyzed the changes from baseline to end point in HDRS-17 total score, which was significantly greater with vilazodone than with placebo (-10.4 ± 0.6 versus -8.6 ± 0.6 , $P=0.022$). Khan et al²¹ reported the HDRS-17 response (defined as $\geq 50\%$ decrease from baseline) was also significantly higher with treatment than placebo over 8 weeks (44.2% versus 32.9%, $P=0.013$). Recently, similar results on the same index were reported, although they did not reach statistical significance (-5.56 versus -4.67 , $P=0.0863$).²⁴ In addition, Robinson et al³⁸ demonstrated that 40 mg per day for 1 year was also safe and well tolerated by adults with MDD.

The unique dual mechanism of action for vilazodone can shorten the onset of antidepressant activity along with enhanced remission and response rates, which may explain the satisfactory clinical efficacy and decreased side effects attributed to serotonin-reuptake inhibition, and provide enhanced benefits for symptoms of anxiety.^{14,15,21}

Side effects, such as diarrhea, nausea, and discontinuations due to AEs, induced by vilazodone were higher than placebo. Gastrointestinal AE incidence in the current study was consistent with observations from vilazodone-registration studies. Similarly to prior studies, most instances of vilazodone-related diarrhea and nausea were mild or moderate in intensity, led to few premature discontinuations, occurred within the first few weeks of treatment, and were transient in nature. Overall, treatment with vilazodone was well tolerated. Furthermore, the incidence of markedly abnormal laboratory or vital sign changes was low and similar between the treatment groups.

The meta-analysis included only studies with all data derived from randomized, double-blind, placebo-controlled

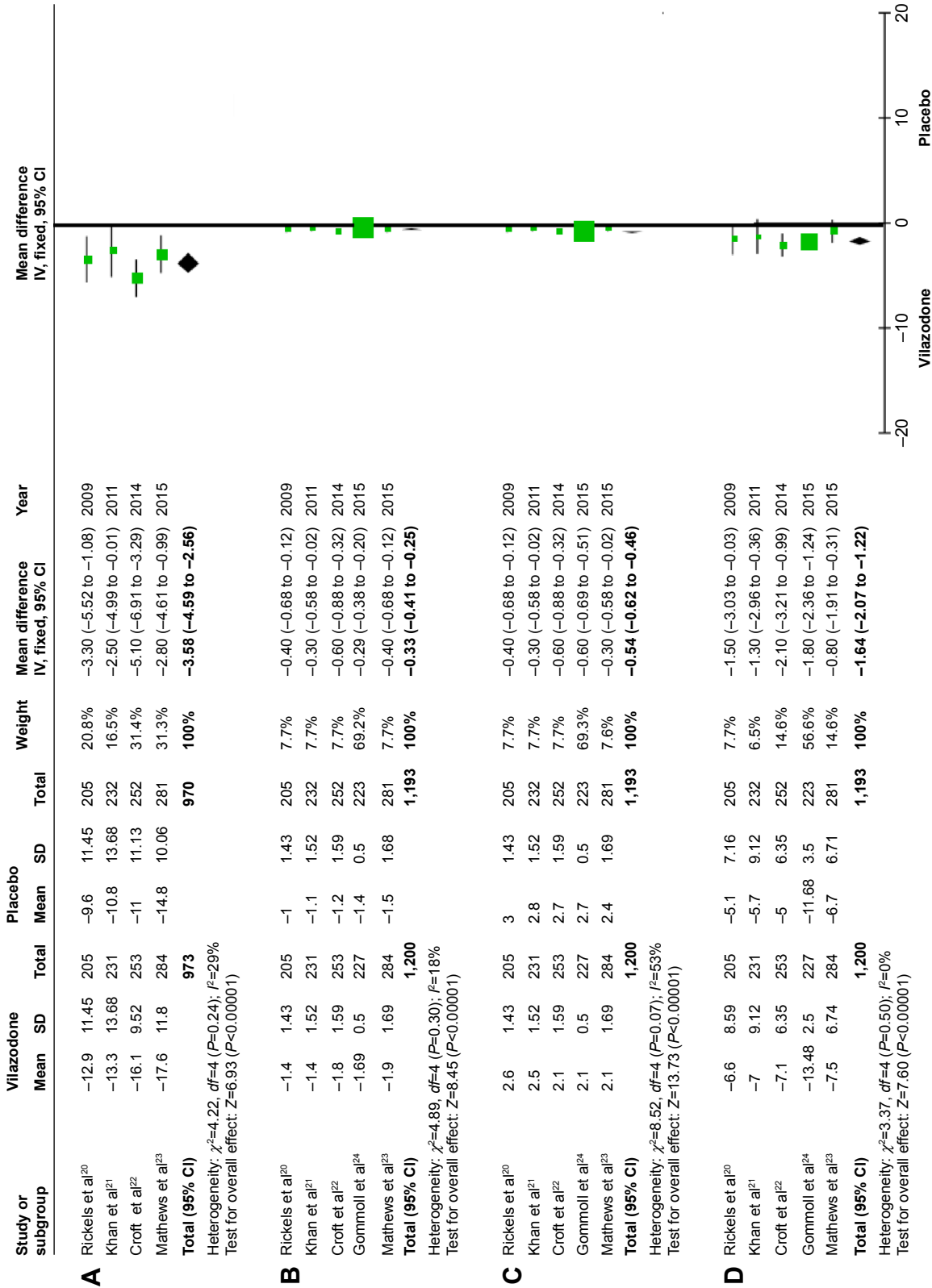


Figure 3 Forest plots showing changes in (A) the MADRS, (B) the CGI-S, (C) the CGI-I, and (D) HAMA in the treatment studies.
Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression - Severity scale; CGI-I, CGI - Improvement scale; HAMA, Hamilton Anxiety Rating Scale; SD, standard deviation; IV, inverse variance; CI, confidence interval.

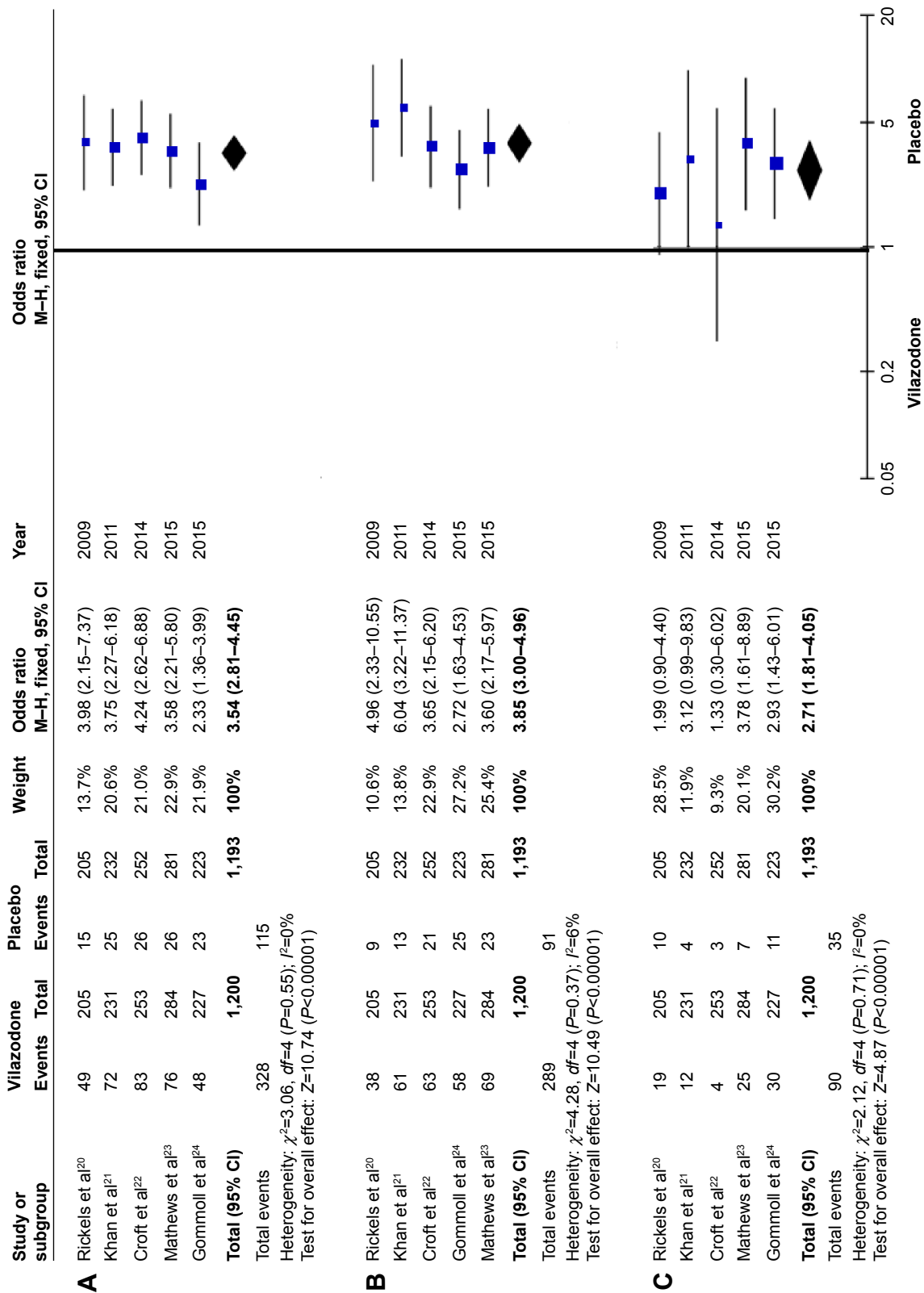


Figure 4 Forest plots showing changes in (A) diarrhea, (B) nausea, and (C) discontinuations due to adverse events. Abbreviations: MH, Mantel-Haenszel; CI, confidence interval.

trials. According to the quality-assessment scale, we confirmed the quality of each study recruited in our analysis. Some limitations of the study should be mentioned. First, the number of included articles was small. Second, the articles did not research the safety and efficacy of vilazodone with longer-term use. Finally, we did not include unpublished studies. Bias may have occurred resulting from these limitations. Larger samples and more high-quality trials are needed to further investigate the efficacy and safety of vilazodone for patients with MDD.

Conclusion

Based on the meta-analysis, we provide further evidence that vilazodone is a safe and effective drug for patients with MDD. It offers promise as a novel oral drug for the treatment of MDD with its superior clinical efficacy and tolerability balance.

Disclosure

The authors report no conflicts of interest in this work.

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