Effectiveness and Safety of Memantine Add-on Treatment for Refractory Obsessive-Compulsive Disorder: A Meta-Analysis

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ABSTRACT

Obsessive–compulsive disorder (OCD) is a highly disabling mental illness characterised by repetitive thoughts and behaviours that disrupt daily life and impair social functioning. The purpose of this meta-analysis was to assess the efficacy and safety of memantine augmentation in treating refractory OCD. This study searched several databases from inception to January 2024 and performed a random-effects meta-analysis with subgroup analyses to evaluate the effects of the dose and duration of the intervention. Seven randomised controlled trials involving 315 participants were included, although significant heterogeneity existed between the studies. Memantine augmentation was significantly superior to a placebo in treating OCD (SMD = -1.17, 95% CI = -2.14 to -0.20, p = 0.02). Subgroup analysis revealed that memantine significantly reduced compulsive behaviours (SMD = -0.99, 95% CI = -1.45 to -0.52, p <0.001). After eight weeks of treatment, the memantine group showed a significant improvement in the total Yale–Brown Obsessive– Compulsive Scale (Y-BOCS) score compared with the placebo group (SMD = -1.06, 95% CI = -1.77 to -0.36, p = 0.003). The memantine group showed a significant improvement in the total Y-BOCS score at a dose of 20 mg/day (SMD = -1.06, 95% CI = -1.77 to -0.36, p = 0.003). Memantine significantly increased the risk of mild rash (relative risk = 7.00, 95% CI = 1.31–37.47, p = 0.02). Memantine is safe and effective for OCD augmentation therapy at 20 mg/day and a continued intervention of at least eight weeks.

Key Words: *Memantine, Obsessive–compulsive disorder, Augmentation, Safety, Efficacy*.

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INTRODUCTION

Obsessive–compulsive disorder (OCD) is a common mental disorder comparable to schizophrenia in terms of disability rate.[1] It is closely related to a higher incidence of dementia, insomnia, digestive system, and circulatory diseases.[2] Epidemiological evidence indicates that the lifetime prevalence of OCD is approximately 1-2%.[3] Serotonin reuptake inhibitors (SRIs) are the medicine of choice for OCD, according to the recommendations of the American Psychiatric Association and current clinical practice;[1] however, 40–60% of patients with OCD respond poorly to SRIs or have residual symptoms.[4] To address this challenge, researchers are actively exploring novel treatments and pharmacological augmentation strategies.

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Recent studies in molecular biology, genetics, and neuroimaging have confirmed abnormalities in glutamatergic neurotransmission as the neurobiological basis of OCD.[5,6] Genetic studies have conclusively demonstrated a strong correlation between the glutamate transporter protein EAAT3, which is encoded by the *SLC1A1* gene, and OCD, offering direct evidence of their association.[7] In addition, proton magnetic resonance imaging studies have shown that striatal glutamate concentrations are higher in patients with OCD than in healthy controls.[8] However, this glutamate-mediated striatal dysfunction is reversible, suggesting that glutamatergic-modulating medicines play a therapeutic role in OCD.[9] Memantine functions as a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor,[10] with the most frequently reported side effects being malaise, dizziness, and drowsiness,[11,12] which are usually transient and mild; therefore, memantine has a high tolerability and safety profile. Currently, memantine is mainly used to treat Alzheimer's disease. It can reduce excessive glutamatergic excitatory activity by blocking NMDA receptor ion channels without affecting normal glutamatergic neurotransmission,[13] and therefore may play a positive role in OCD treatment.

Recently, scientists have attempted to combine memantine with first-line therapeutic agents for the treatment of OCD, and some open or controlled trials have shown good efficacy.[14,15]

Although some meta-analyses on related topics have been published, the quality of evidence requires improvement. For example, in 2018, Kishi *et al*.[16] included three randomised controlled trials (RCTs) involving 114 patients with OCD, showing that antidepressants combined with memantine were beneficial for OCD treatment; however, the small sample size may have led to biased results. Modarresi *et al*. found memantine to be effective in improving moderate-to-severe OCD, with the main limitation being the inclusion of open-label studies.[17] The 2021 study by Hadi *et al*. combined the efficacy of multiple medicines such as memantine, minocycline, riluzole, and other glutamatergic medications, which may affect the reliability and generalisability of the conclusions, and there is a lack of systematic evaluation of memantine as an adjunctive treatment for OCD.[18]

Ultimately, given the current lack of clinical evidence on memantine augmentation in the treatment of OCD, there remains some uncertainty regarding the ideal dose and duration of the intervention. This systematic review aimed to provide a comprehensive and extensive assessment of the efficacy and safety of memantine in the treatment of OCD by analysing randomised controlled studies, resulting in a meta-analysis that offers an up-to-date, evidence-based foundation for clinical practice.

METHODOLOGY

This study strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The authors searched the literature published in PubMed, Web of Science, China National Knowledge Infrastructure, Cochrane Library, and Embase since their inception up to January 2024 with the keywords ("Obsessive-compulsive disorder" OR "obsess" OR "OCD") AND ("Randomised controlled trial" OR "RCT" OR "controlled trial") AND (Memantine).

The inclusion criteria were participants fulfilling the OCD diagnostic criteria as stipulated in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), irrespective of their age, gender, or ethnicity; an outcome indicator of Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) and a score of ≥15 points; the intervention was the use of memantine augmentation for the treatment of OCD, and studies being randomised controlled trials (RCT). The criteria for exclusion were studies in which participants had a previous history of NMDA receptor antagonist use, abstracts, conferences, posters, and duplicates of the published literature, as well as uncompleted clinical trials.

Two authors performed independent literature screening and data extraction for the included studies. The extracted data included study characteristics (year of publication, authors, and country), participant characteristics (number of participants, gender, and age), interventions (medications used and dosage), intervention duration, outcome indicators, Y-BOCS scores before and after the intervention, and number of adverse events. When dealing with continuous outcome data, the data extraction process exhaustively documented the mean amount of change from baseline levels, and the corresponding standard deviation, and indicated the number of valid participants in each study when endpoints were assessed for each outcome indicator. For the measurement of dichotomous outcome data, the emphasis was placed on sample size statistics for each group, with special attention paid to the counts of adverse events and their statistical treatment to ensure the comprehensiveness and accuracy of the data. Divergences were assessed by a third reviewer, and final decisions were made through discussion.

The primary outcome measure was the standardised mean difference (SMD) in Y-BOCS scores before and after intervention in the experimental and control groups, and the secondary outcome was adverse events. The Y-BOCS is considered a reliable and valid measure of OCD severity and is used to assess the baseline level of OCD symptoms and monitor changes over time, including response to treatment.[20] It is divided into two main parts: The obsessions scale and the compulsions scale. The obsession subscale assesses the severity of the patients' obsessions. It includes questions related to the time occupied by obsessive thoughts, the degree of interference these thoughts have on the person's life, the distress they cause, and the degree of control the person has over these thoughts. The compulsion subscale evaluates the severity of a patient's compulsive behaviour. Similar to the obsessions scale, it includes items that measure the time spent on compulsive behaviours, the distress associated with the compulsions, and the level of control over these compulsive actions. The total Y-BOCS score, which ranges from 0 to 40, is calculated by summing the scores of the obsessions and compulsions scales.[21] Higher scores indicate more severe OCD symptoms.

Two authors evaluated the studies included in the review utilising the risk of bias tool developed by the Cochrane Collaboration. The tool covers random sequence generation, double blinding (participant and staff), blinding of outcome assessors, allocation concealment, missing data, selective reporting, and potential bias, each of which is assessed as low risk (yes), high risk (no) or unknown risk (unclear).

The data from the literature was analysed using RevMan5.3 software. As recommended by Morris, SMD was calculated using the mean and standard deviation of Y-BOCS scores before and after the intervention to minimise bias and enhance precision.[22] For each outcome measure, 95% confidence intervals (CIs) were presented, with a p-value threshold of <0.05 deemed significant. The I^2 statistic was utilised to assess heterogeneity. According to the guidelines of the Cochrane handbook for systematic reviews of interventions, this study defined an I^2 value greater than 50% as substantial heterogeneity. It is advisable to employ a random-effects model for the analysis and, if needed, perform a sensitivity analysis to assess the robustness of the findings. In sensitivity analyses, differences in region, age range, Y-BOCS score, gender ratio, and baseline treatment medication were specifically considered.

This study conducted three subgroup analyses, the effect of memantine augmentation therapy on the two core symptoms of OCD, the effect of memantine dose on OCD, and the effect of memantine intervention duration on OCD. Compulsive

behaviour and obsessive thoughts are the core symptoms of OCD. Obsessive thoughts were assessed by the obsessions scale and compulsive behaviours by the compulsions scale. The Y-BOCS total score was used to determine the effect of different doses of memantine and different intervention durations on OCD symptoms.

RESULTS

A preliminary search identified 171 relevant studies, subsequently eliminating 31 duplicates. After assessing the titles and abstracts, 91 studies were disqualified, narrowing the pool to 49 candidates. These remaining studies underwent comprehensive full-text evaluation against the prescribed selection criteria. The study selection process is shown as a PRISMA diagram (Figure 1). Ultimately, this meta-analysis encompassed a total of seven studies involving 315 participants.[23-29] Table I displays the main features of the studies included. This study conducted a quality assessment of the seven included studies and found that four studies did not specify how allocation concealment was implemented,[23,24,27,28] e.g., the studies did not report whether a central randomisation system or closed opaque envelopes were used, and one study did not state whether researchers and participants were blinded.[23] Quality assessments are shown in Figure 2.

Among the seven included RCTs, six utilised SRI as the baseline medication,[23,25-29] and one utilised mood stabilisers.[24] Upon conducting a heterogeneity test, this study revealed a significant I^2 value of 85% among the seven included studies, indicative of considerable heterogeneity. Sensitivity analysis showed that none of the studies had an impact on the findings. Consequently, this study employed a random-effects meta-analysis to address this heterogeneity. The results of this meta-analysis showed that the difference in the changes in the Y-BOCS scores between the memantine and placebo groups was statistically significant (SMD = -1.17, 95% CI = -2.14 to -0.20; p = 0.02, Figure 3).

The effects of memantine compared with placebo on compulsive behaviours and obsessive thoughts were assessed after controlling for the duration and dose of the intervention. Three studies provided information on the obsession and compulsion subscales.[23,25,27] While the memantine group did not exhibit a statistically significant difference in obsession subscale scores compared to the placebo group (SMD = -0.88, 95% CI -1.80 to -0.03; p = 0.06), a statistically significant difference was observed in the change of compulsion subscale scores (SMD = -0.99, 95% CI -1.45 to -0.52, p <0.001, Figure 4A).

Table I: Basic characteristics of the included literature.

Study	Region	Memantine group				Control group			Minimum Y-BOCS for inclusion
		Intervention	Sample	Age, mean (SD)	Gender (female %)	Sample	Age, mean (SD)	Gender (female %)	
Askari *et al*.[29] 2022	Iran	Sertraline (200mg/d) + Memantine (20mg/d)	35	35.0 ± 11.3	77.1%	30	34.8 ± 10.3	56.7%	≥21
Modarresi *et al*.[25] 2018	Iran	SRI + Memantine (20mg/d)	15	30.6 ± 6.8	60%	15	30.7 ± 4.7	67%	≥24
Sahraian *et al*.[24] 2017	Iran	Routine medications (Lithium +Olanzapine) +Memantine (20mg/d)	19	34.2 ± 10.2	68.42%	19	34.2 ± 10.2	63.15%	≥17
Jun *et al*.[23] 2019	China	Sertraline (150-200mg/d) OR Fluvoxamine (200-300mg/d) OR Fluoxetine (50-60mg/d) + Memantine (20mg/d)	24	28.8 ± 2.6	70.8%	25	29.0 ± 2.8	68%	≥24
Farnia *et al*.[28] 2018	Iran	Fluoxetine (40mg) + Memantine (10mg/d)	33	29.9 ± 5.2	48.5%	33	29.9 ± 5.4	51.5%	≥15
Ghaleiha *et al*.[27] 2013	Iran	Fluvoxamine (100mg/d) + Memantine (20mg/d)	19	36.2 ± 6.0	65%	19	37.5 ± 6.2	74%	≥21
Haghighi *et al*.[26] 2013	Iran	Escitalopram (10mg/d) OR Citalopram (30-50mg/d) OR clomipramine (100-175mg/d) + Memantine (10mg/d)	14	30.8 ± 6.0	85.7%	15	31.6 ± 5.1	73.3%	

Note: SRI = Serotonin re-uptake inhibitors.

Table II: Summary results for adverse events.

Outcomes	RR (95% CI)	p-value	I^2 (%)	p-value for heterogeneity
Headache	1.08 (0.48-2.41)	0.85	0	0.94
Decreased appetite	1.27 (0.43-3.81)	0.67	0	0.96
Insomnia	1.84 (0.33-10.15)	0.49	43	0.18
Rash	7.00 (1.31-37.47)	0.02	34	0.22
Dizziness	1.12 (0.43-2.90)	0.81	0	0.80
Constipation	0.74 (0.37-1.48)	0.39	0	0.67
Nausea	1.09 (0.45-2.65)	0.85	0	0.83
Total	1.22 (0.85-1.73)	0.28	0	0.98

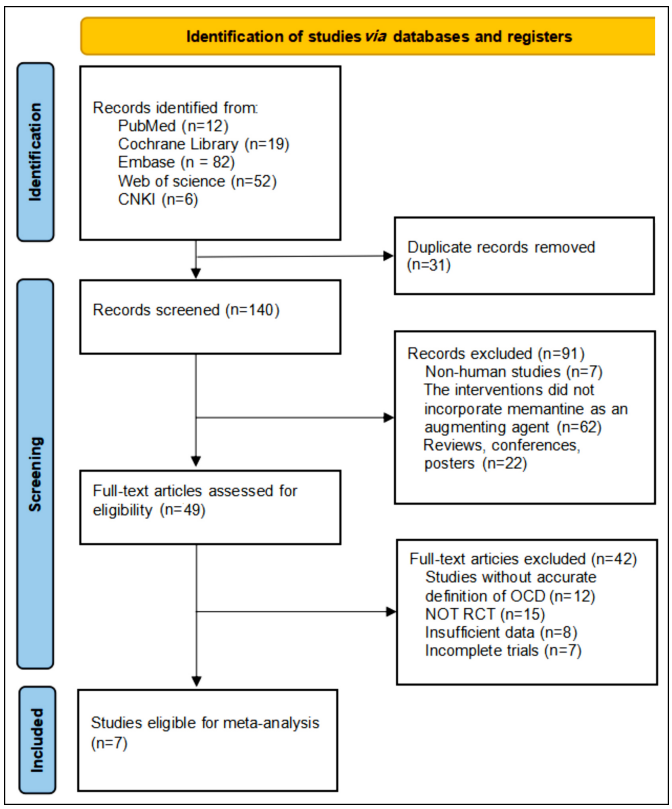

Figure 1: Flowchart of literature screening.

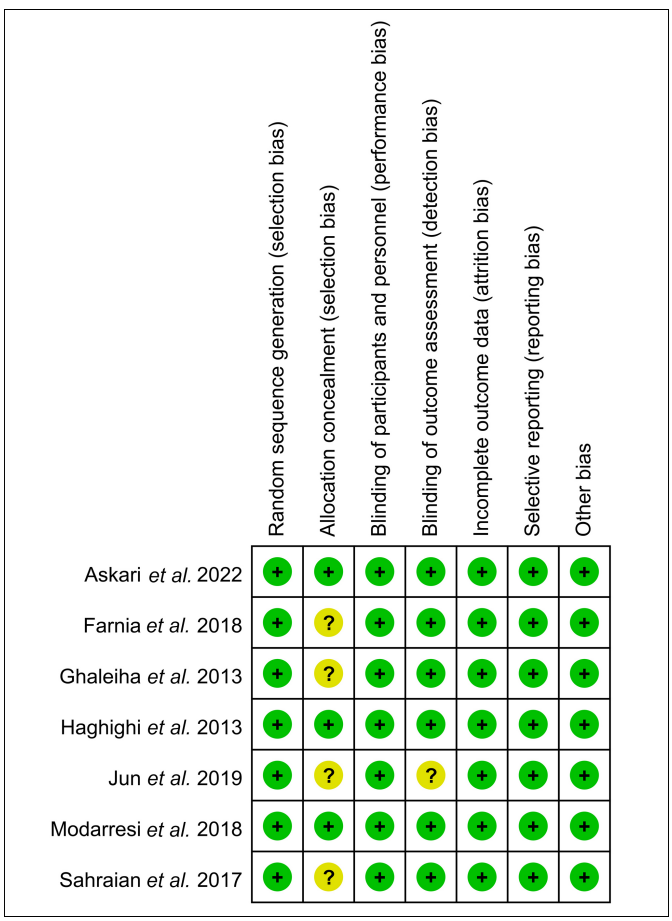

Figure 2: Evaluation chart of the quality of the included literature.

After controlling for the dose of memantine, this study compared the effects of different intervention durations on the effect of treatment in patients with OCD. Five studies provided data from intervention to week 4,[23-25,27,29] four provided data from intervention to week 8,[23-25,27] and three provided data from intervention to week 12.[23,25,29] Compared to the placebo group, the difference in the total Y-BOCS score change values was not statistically significant in the memantine group at week 4 (SMD = -0.12, 95% CI -0.57 to 0.32; p = 0.58). This difference was statistically significant in the memantine group at week 8 (SMD = -1.06, 95% CI -1.77 to -0.36; p = 0.003). At week 12, the change value in the total Y-BOCS score in the memantine group was not statistically significant (SMD = -1.73, 95% CI -4.17 to 0.72; p = 0.17, Figure 4B).

After controlling for the duration of the intervention, this study compared the effects of different memantine doses on the outcome of patients with OCD. Two studies used memantine at a dose of 10 mg/day,[25,26] and four at 20 mg/day.[23-25,27] Compared with the placebo, the difference in the change value of the total Y-BOCS score was not statistically significant at a memantine dose of 10 mg/day (SMD = -0.08, 95% CI -0.82 to 0.66; p = 0.83). However, it was statistically significant at a memantine dose of 20 mg/day (SMD = -1.06, 95% CI -1.77 to -0.36; p = 0.003, Figure 4C).

The summary results of adverse events are presented in Table II. The use of memantine augmentation for the treatment of OCD increased the risk of developing a mild rash (relative risk [RR] = 7.00, 95% CI = 1.31–37.47, p = 0.02). However, it did not significantly affect the risk of headache (RR = 1.08, 95% CI = 0.48–2.41, p = 0.85), decreased appetite (RR = 1.27, 95% CI = 0.43–3.81, p = 0.67), nausea (RR = 1.09, 95% CI = 0.45–2.65, p = 0.85), insomnia (RR = 1.84, 95% CI = 0.33–10.15, p = 0.49), dizziness (RR = 1.12, 95% CI = 0.43–2.90, p = 0.81), and constipation (RR = 0.74, 95% CI = 0.37–1.48, p = 0.39, Figure 5).

DISCUSSION

This study suggests that memantine augmentation has a positive effect on alleviating OCD symptoms, indicating its potential as an effective treatment option. While significant heterogeneity was observed across studies, the overall evidence points to the beneficial role of memantine in OCD treatment. The safety profile of memantine was also favourable, with only a mild rash being reported, and no increased risk of other adverse events, suggesting that it is generally well-tolerated.

Memantine is a glutamatergic medicine that modulates abnormally activated neurotransmission and restores glutamatergic neurons to their resting state.[30] Animal studies have shown the synergistic effects of SRI and memantine in improving compulsive scratching in mice, with therapeutic efficacy superior to that of SRI alone.[31]

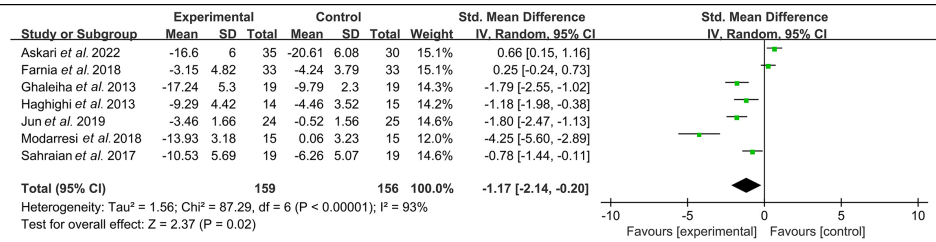

Figure 3: Forest plot of changes in Y-BOCS scores before and after treatment in the memantine group versus the placebo group.

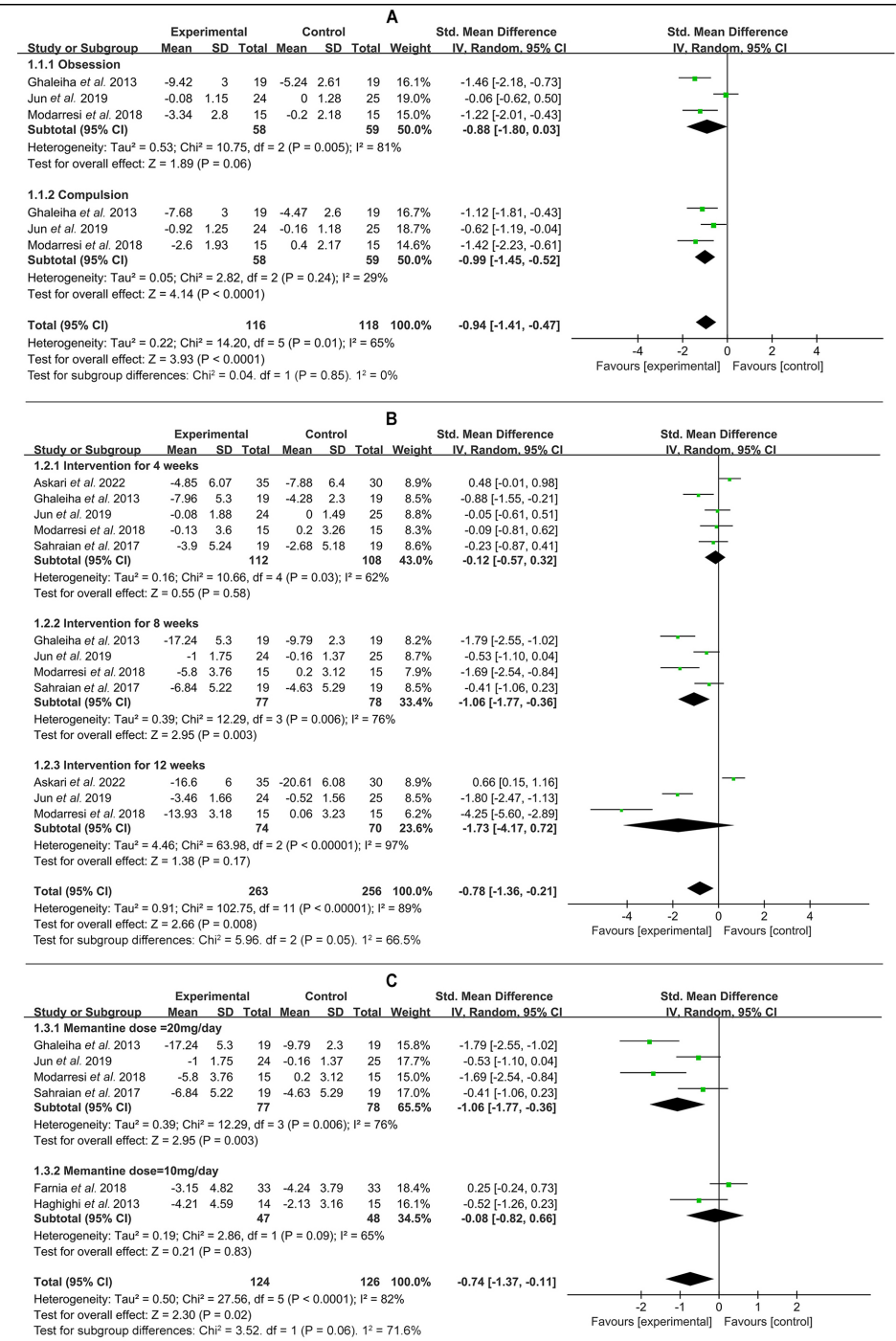

Figure 4: Effect of memantine on OCD in randomised, double-blind, and placebo-controlled trials. (A) Subgroup analysis of the two dimensions of OCD. (B) Subgroup analysis of different durations. (C) Subgroup analysis of different dosages.

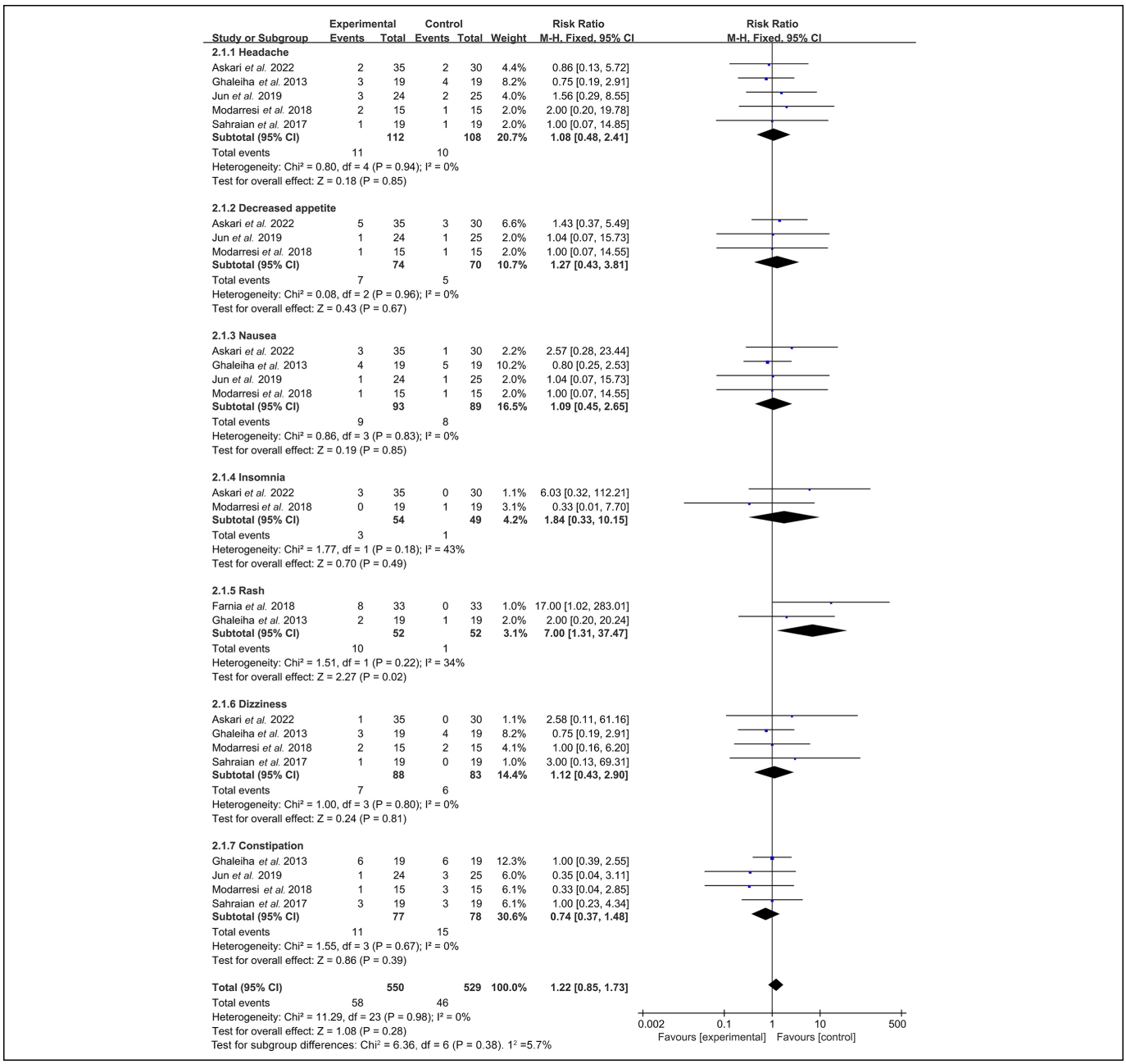

Figure 5: Summary results for adverse events.

An open trial conducted by Bakhla *et al*.[14] further demonstrated that the use of memantine in patients with OCD is safe, with a reduction of over 25% in total Y-BOCS scores following 12 weeks of continuous intervention. In conclusion, memantine demonstrates excellent potential as an augmentation therapy for OCD in clinical settings.

This study provides the first comprehensive analysis of the therapeutic effect of memantine on obsessive thoughts and compulsive behaviours. The results showed that memantine significantly reduced compulsive behaviours compared with placebo. By contrast, memantine showed a trend towards improvement in obsessive thoughts but did not reach a significant level. These results may be influenced by several factors. First, compulsive behaviours are often easier to observe and quantify than obsessive thoughts. Second, some studies based on the neural circuits in OCD have suggested that compulsive behaviours may be more related to prefrontal cortex-striatum circuits, while obsessive thoughts may involve the dorsal prefrontal cortex-amygdala-cingulate cortex loop.[32-34] The effects of memantine are primarily focused on the CSTC loop; thus, its effect on obsessive thoughts may be limited. In addition, compared to compulsive behaviours, obsessive thoughts are more influenced by cognitive factors, such as thought patterns and belief systems, which may require co-intervention in conjunction with CBT and longer treatment duration to effect change.

This study found that, based on the original medication treatment, after adding a dosage of 20 mg/day of memantine, there was no improvement in the total Y-BOCS score at the end of the 4th week. However, a significant decrease in the total Y-BOCS score was noted by the end of the 8th week. Although there was a trend of improvement in the total Y-BOCS score by the end of the 12th week (SMD = -1.73), it was not statistically significant. This suggests that in the first four weeks after adding memantine, the medicine's concentration might not have been sufficient for symptom improvement. As the medicine gradually accumulated in the body, it reached an effective therapeutic concentration by the end of the 8th week, showing increasingly positive effects. The lack of significant improvement at the end of the 12th week may be due to the number of included RCTs influencing the results. Two of the included RCTs indicated that memantine started showing efficacy in treating OCD by the 8th week and achieved significant remission at the end of the 12th week.[23,25] However, one RCT showed that the 12th-week intervention was ineffective in improving OCD symptoms,[29] possibly affecting the significance of the overall result. These findings are consistent with those of previous meta-analyses. A meta-analysis published in 2019 suggested that if patients with OCD do not respond after eight weeks of memantine augmentation treatment, extending the intervention to 12th weeks is recommended.[17] In summary, an intervention period of eight weeks is a crucial assessment point. However, if no improvement is observed during this period, this does not necessarily mean that the treatment is ineffective. Extending the treatment period to 12th weeks might be necessary to observe significant improvements. Additionally, assessing patients weekly during treatment is recommended to precisely monitor the effects.

This study further analysed the efficacy of different memantine doses in patients with OCD. These findings indicated that a 10 mg/day dose showed a slight but statistically insignificant decrease in the total Y-BOCS score, while a 20 mg/day dose led to a statistically significant decrease. Previous meta-analyses have found that <20 mg/day and 20 mg/day doses of memantine significantly reduced Y-BOCS scores, with the latter having a more significant ameliorative effect. However, this study included an open trial, which may have biased the outcomes.[17] The study by Sahraian *et al*. suggests that, compared to a placebo, memantine augmentation treatment can effectively improve OCD symptoms in patients with manic episodes of bipolar disorder (BD), with no significant adverse effects.[24] This suggests that whatever medication is augmented with memantine, has the potential to have a beneficial effect on OCD symptoms.[35] Given the prevalence of BD and OCD comorbidities and the potential exacerbation of BD symptoms by SRIs, memantine could be a promising therapeutic strategy to improve OCD symptoms in patients with BD, warranting further investigation in more extensive randomised trials. In summary, this study provides a reference for the treatment of OCD using memantine.

This study has a few limitations. First, the inclusion of a limited number of RCTs suggests potential research constraints and publication bias. Four studies did not specify whether allocation concealment was implemented, which poses a potential risk of operational bias in the randomisation process. Future research should focus on the transparent reporting of methodological details to enhance the quality of studies. Second, six of the seven included studies were conducted in Iran, with only one from China. The lack of regional diversity, while potentially reducing heterogeneity, also limits the external validity of the findings and hinders the feasibility of conducting subgroup meta-analyses based on geographic regions. Lastly, the small number of RCTs in this field restricted subgroup analyses based on baseline characteristics, such as Y-BOCS scores, age, gender ratio, and baseline treatment medication, which are likely the main sources of heterogeneity. Future research should prioritise the inclusion of a larger and more diverse sample of RCTs that address these baseline characteristics. Additionally, conducting studies across different cultural and healthcare settings could further enhance the generalisability of the findings.

CONCLUSION

Memantine is safe and effective for treating OCD without serious adverse events. Augmenting first-line pharmaco-therapy with 20 mg/day of memantine for at least eight weeks effectively treats OCD, particularly in improving compulsive behaviours.

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DATA AVAILABILITY:
This protocol was registered with the International Prospective Register of Systematic Reviews under the protocol (ID CRD42024495982).

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
WZ: Conceptualisation, methodology, software, investi-gation, formal analysis, and writing of the original draft.
YZ: Data curation and writing of the original draft.
EY: Conceptualisation, funding acquisition, resources, supervision, writing, review, and editing.
All authors approved the final version of the manuscript to be published.

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