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Review article

A systematic review and meta-analysis: Memantine augmentation in moderate to severe obsessive-compulsive disorder

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ABSTRACT

A considerable proportion of obsessive-compulsive disorder (OCD) patients receiving first-line pharmacological therapy, fail to fully respond to treatment and continue to exhibit significant symptoms. In this systematic review, we evaluate the efficacy of memantine, as a glutamate-modulating agent, in moderate to severe OCD.

Single and double blinded as well as open-label trials of memantine augmentation in adults with OCD were considered. Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores were the primary outcome measure. The electronic databases of PubMed, Scopus, Embase and Google Scholar were searched for relevant trials using keywords 'obsessive-compulsive disorder OR OCD' AND 'memantine'.

The meta-analysis of eight studies involving 125 OCD subjects receiving memantine augmentation exhibited a significant overall mean reduction of 11.73 points in Y-BOCS scores. The categorical analysis of treatment response (a minimum of 35% reduction in Y-BOCS) in four double-blind placebo-controlled studies indicated that OCD patients receiving memantine augmentation were 3.61 times more likely to respond to treatment than those receiving placebo.

We found that 20 mg/day memantine augmentation to first-line pharmacological treatment for a period of at least 8 weeks is a safe and effective intervention for moderate to severe OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common and debilitating neuropsychiatric disorder worldwide and is characterized by recurrent obsessions and compulsions that cause marked distress to the afflicted individuals (Rabe-Jablonska and Bienkiewicz, 1994). Patients with OCD are at risk of serious social disability and impairment in work performance (Pittenger et al., 2005). Serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy (CBT) are considered as first line approaches for OCD, however symptoms often persist and full remission is uncommon (Ackerman and Greenland, 2002; Mataix-Cols et al., 2002). Several pharmacological augmentation strategies have been implemented to aid patients non-responding to SRI monotherapy (Coric et al., 2005; Denys et al., 2004; Feusner et al., 2009; Hollander and Dell'Osso, 2006; Koran et al., 2005; Lafleur et al., 2006; Li et al., 2005). The most common category of augmentation agents includes antipsychotics which act on serotonergic-dopaminergic systems; however, patients often experience intolerable adverse effects (Bloch et al., 2012; Veale et al., 2014).

Recent studies suggest a role for increased glutamate levels in cerebrospinal fluid, glutamatergic over-activity, and polymorphism of gene coding N-methyl-D-aspartate (NMDA) receptor in the pathophysiology of OCD (Albelda et al., 2010; Aouizerate et al., 2004; Arnold et al., 2004; Zdanys and Tampi, 2008). There is a large body of evidence on the clinical benefits of augmentation therapy with glutamate-modulating agents such as riluzole, N-acetylcysteine, ketamine, memantine and amantadine in reducing symptoms in SRI resistant OCD (Afshar et al., 2014; Bloch et al., 2012; Coric et al., 2005; Lafleur et al., 2006; Paydary et al., 2016; Stryjer et al., 2014).

Memantine is a specific, noncompetitive antagonist at the NMDA receptor that blocks sustained activation of the NMDA receptor and may thus reduce excessive cortico-striatal glutamate transmission in OCD (Bormann, 1989; Mobius, 2003; Reisberg et al., 2003). It also enhances intracortical inhibition, which is deficient in OCD (Greenberg et al., 2000). Memantine is approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease and is

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reported to be safe and well tolerated (Ferguson and Shingleton, 2007; Keck et al., 2009; Zdanys and Tampi, 2008). Its most commonly reported adverse effects include dizziness, somnolence, confusion and headache, that are usually mild and transient (Amidfar et al., 2016; Wu et al., 2012).

Several open label and controlled trials have been conducted in the past decade to evaluate the efficacy of memantine augmentation in the treatment of moderate to severe OCD and the majority of studies have yielded promising outcomes (Bakhla et al., 2013; Feusner et al., 2009; Ghaleiha et al., 2013; Haghighi et al., 2013; Modarresi et al., 2018; Rodriguez et al., 2016; Sahraian et al., 2017). A limited meta-analysis has recently been conducted involving only three double-blinded placebo-controlled trials of memantine augmentation in OCD treatment (Kishi et al., 2018). The response rate was evaluated, exhibiting a significant effect for memantine augmentation. The present study is a broader systematic review and meta-analysis and examines the efficacy of memantine as an augmentation strategy for moderate to severe OCD in recently conducted, single and double blinded as well as open-label trials.

1.1. Objective

- To evaluate and systematically review evidence of the efficacy of memantine augmentation in reducing OCD symptom severity amongst moderate to severe adult OCD patients who were concurrently receiving a first-line pharmacological treatment;
- To determine if the mean difference in Y-BOCS ratings were influenced by:
  - SRI-refractoriness of OCD patients;
  - Dose of memantine augmentation;
  - Presence of comorbid disorders in OCD patients;
  - Length of treatment with memantine augmentation;
- To evaluate evidence of the efficacy of augmentation with memantine compared to placebo in inducing clinical response among moderate to severe OCD patients who were concurrently receiving SRI monotherapy.

2. Methods

The review aimed to consider any single or double blinded as well as open-label study that investigated the effects of memantine in adults with OCD.

2.1. Eligibility criteria

Studies were included if: (1) they described adults (>18 years) who had a diagnosis of OCD according to Diagnostic and Statistical Manual of Mental Disorders (DSM); (2) they used the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) as a measure of OCD severity before and following treatment with memantine (Goodman et al., 1989). The Y-BOCS is a 10-item clinician-rated scale which is widely used to measure the severity of obsessive-compulsive symptoms, which has a total score of 0 to 40. Higher scores indicate more severe OCD symptoms; (3) participants had moderate to severe symptoms of OCD defined as a Y-BOCS score of 16 or more (Goodman et al., 1989); (4) they had a trial end-point of at least 8 weeks.

We excluded studies involving participants with a history of treatment with NMDA glutamate receptor antagonist (Rodriguez et al., 2016).

2.2. Information sources and search procedure

The electronic databases of PubMed, Scopus, Embase and Google Scholar were searched for relevant trials. The medical subject headings (MeSH) used were 'obsessive-compulsive disorder OR OCD' AND 'memantine'. The search results were limited to adults aged over 18. The reference lists of yielded articles were also screened for additional published reports and citations of unpublished research. Clinical trial registries including International Clinical Trials Registry Platform (who.int) and clinicaltrials.gov were also included in the search procedure.

2.3. Outcome measures

Our primary outcome measure (effect size) was the mean difference in Y-BOCS rating before and after pharmacological intervention in OCD patients receiving memantine. The secondary outcome measures, evaluated considering only the double-blind placebo-controlled trials, were (a) the mean difference in Y-BOCS rating and (b) the proportion of treatment responders in the memantine augmentation group compared to the placebo group. A 35% decline in Y-BOCS rating was chosen as the threshold for treatment response based on the definition of full treatment response suggested by the International Treatment Refractory OCD Consortium (Goodman et al., 1989).

2.4. Subgroup analysis and meta-regression

The following subgroup analyses of mean Y-BOCS change were carried out:

- Stratification by SRI-refractory OCD: (1) refractory; and (2) non-refractory.
- Stratification by memantine target dose: (1) less than 20 mg/day, and (2) 20 mg/day
- Stratification by the presence of comorbid disorders: (1) with comorbidity, and (2) without comorbidity.

Meta-regression was used to test the assumption whether a linear relationship existed between the mean Y-BOCS change and duration of memantine therapy.

2.5. Study selection

A full-text article was retrieved for any study deemed relevant by any of the reviewers. Two reviewers (AM and SCH) independently identified and selected the studies to be included in this review by using the eligibility criteria stated above.

2.6. Data collection process

Information was extracted by two independently working reviewers from each included study on methods, participants, intervention, outcome measurements and other relevant attributes and results of the studies. The methodological quality of each trial was assessed in accordance with the Cochrane risk-of-bias criteria in the Cochrane Handbook (Higgins et al., 2011). Missing data were obtained from study investigators whenever possible. When end-point Y-BOCS rating was not available, we used Y-BOCS change data in the analysis (Bakhla et al., 2013; Stewart et al., 2010).

We calculated difference in Y-BOCS means (pre and post) for each study and change-from-baseline standard deviation by following Cochrane guidelines on how to impute missing standard deviations using Pearson's correlation coefficient r. It was possible to calculate $r = 0.25$ from the statistics output of one of the articles included in the meta-analysis (Feusner et al., 2009). Therefore, our Pearson's r value from which to compute the change standard deviation was kept at 0.25 based on previous research.

2.7. Systematic review and meta-analysis methods

Analyses were conducted in STATA, version 11. For all outcome measures, 95% confidence intervals were reported and p value of

<0.05 was considered as significant. For all continuous outcome measures, a random effects meta-analysis model of continuous data, with each study weighted by the inverse of the variance was utilized (DerSimonian and Laird, 1986). Forest plots were created, each line depicting estimates and confidence intervals (CI) for each study, and plotting (square) symbol size representing the weight of each study entered into the analysis.

A categorical meta-analysis was conducted to determine the risk ration (RR) for proportion of treatment responders in memantine versus placebo groups. The number needed to treat (NNT) was also reported for this outcome measure as this statistic is the most clinically relevant when considering memantine augmentation in OCD patients. Two of the studies found 0 responders in the placebo group (Haghighi et al., 2013; Modarresi et al., 2018). STATA performs poorly for studies with a very low or very high event rate and so by default replaces 0 frequencies by 0.5 in order to give a minimum variance unbiased estimate. As this procedure can influence weighted mean differences, the categorical analysis is to be considered with caution.

Heterogeneity across studies was assessed visually with the Frost plot and statistically with the I^2 heterogeneity statistic ($I^2 > 50$ was regarded as considerable heterogeneity) (Higgins et al., 2011). Asymmetry and publication bias of the data was assessed by a Funnel plot. However, the small number of studies and participants for each trial made it difficult to interpret (Veale et al., 2014). Stratification of results by subgroup comparisons and meta-regression examined various obvious sources of heterogeneity within our study sample.

2.8. Included studies

According to the search procedure, 20 studies were screened for eligibility and subsequently based on the inclusion/exclusion criteria, eight studies were considered in the review. A recent double-blind placebo-controlled trial was identified which showed no benefit from adding memantine (Farnia et al., 2018). However, this trial did not meet our inclusion criteria for moderate to severe OCD subjects (Y-BOCS $\geq$ 16). No unpublished studies were found from trial registries.

Of the eight studies included in this review, four were double-blind, randomised, placebo-controlled trials, one was a single blinded case-control trial and three were open-label studies. All studies used Y-BOCS ratings as the primary measure of OCD symptom severity. Three of these eight studies included SRI-refractory OCD subjects who had failed at least 12 weeks of SRI therapy (Aboujaoude et al., 2009; Bakhla et al., 2013; Modarresi et al., 2018). Despite the title of Haghighi et al. implies that SRI-refractory patients were assessed, it was stated in the discussion section that all recruited OCD subjects received treatment for the first time (Haghighi et al., 2013). Thus, this study was not considered as SRI-refractory OCD. Three studies included OCD patients with comorbid disorders (Aboujaoude et al., 2009; Sahraian et al., 2017; Stewart et al., 2010). A full description of the eight included studies in this review is given in Table 1. Ghaleiha et al. gave the end-point Y-BOCS scores in a bar chart from which it was not possible to obtain the precise scores (Ghaleiha et al., 2013). The authors were contacted who provided the end-point data.

3. Results

3.1. Risk of bias across the studies

A Funnel plot for all the studies is shown in Fig. 1, which shows an extent of asymmetry. However, since all studies included in the analysis were small, it is difficult to make a firm conclusion in terms of small study bias. Asymmetries in Funnel plots can also be due to heterogeneity within the sample and over-estimation of treatment in some studies. The I^2 values indicate that there was significant heterogeneity between the double-blind placebo-controlled trials (Figs. 6 and 7). However, the small number of trials means that the estimate may not be reliable.

All trials had a small sample size. There were no long-term follow-up data. Two studies did not report any dropouts (Bakhla et al., 2013; Feusner et al., 2009), two studies used intention-to-treat (ITT) analysis with last observation carried forward (LOCF) for missing data (Aboujaoude et al., 2009; Stewart et al., 2010), two studies used modified intention-to-treat (mITT) analysis by excluding participants who did not have any postrandomization assessment (Ghaleiha et al., 2013; Modarresi et al., 2018), and two studies used per protocol analysis by excluding patients who did not complete the study (Haghighi et al., 2013; Sahraian et al., 2017). Although post-randomization exclusion by mITT and per protocol analyses is known to produce bias (Nuesch et al., 2009; Tierney and Stewart, 2005), the potential magnitude and direction of bias is unknown.

Given the above risks of bias, we would advise caution in any conclusion of publication bias.

3.2. Mean reduction of Y-BOCS score

All eight studies including 125 subjects receiving memantine augmentation contributed to this analysis (see the Forest plot in Fig. 2). The overall mean reduction in Y-BOCS score after at least 8 weeks of memantine augmentation was 11.73 (95% CI: 8.34–15.12, $p < 0.001$) points. This was equivalent to 39.5% reduction in the mean baseline Y-BOCS score.

3.3. Subgroup and meta-regression results

All eight studies including 125 subjects contributed to subgroup and meta-regression analyses:

3.3.1. Mean reduction of Y-BOCS score stratified by SRI-refractory OCD

Fig. 3 is a Forest plot demonstrating the overall mean reduction of Y-BOCS score stratified by refractoriness of OCD patients. Three studies involving 41 subjects followed OCD patients who had been treated with at least 12 weeks of SRI monotherapy at the maximum-tolerated dose before augmentation (Aboujaoude et al., 2009; Bakhla et al., 2013; Modarresi et al., 2018). Stratification based on refractoriness to SRI treatment before memantine augmentation revealed that both subgroups exhibited significant reduction in the mean Y-BOCS score: 12.17 (95% CI: 7.52–16.81, $p < 0.001$) in refractory OCD patients, and 11.24 (95% CI: 6.27–16.20, $p < 0.001$) in non-refractory OCD patients.

3.3.2. Mean reduction of Y-BOCS score stratified by dose of memantine augmentation

Stratification based on dose of memantine augmentation showed that both subgroups exhibited significant effect size, but OCD patients receiving a target dose of 20 mg/day (Aboujaoude et al., 2009; Feusner et al., 2009; Ghaleiha et al., 2013; Modarresi et al., 2018; Sahraian et al., 2017) appeared to demonstrate a more favourable response as compared to patients receiving <20 mg/day dose (Bakhla et al., 2013; Haghighi et al., 2013; Stewart et al., 2010). The former group exhibited 13.15 (95% CI: 8.96–17.35, $p = 0.002$) points of mean reduction in Y-BOCS score while the latter group exhibited 9.05 (95% CI: 3.29–14.81, $p < 0.001$) points reduction. The Forest plot of this subgroup comparison is shown in Fig. 4.

3.3.3. Mean reduction of Y-BOCS score stratified by comorbid symptoms

Three studies recruited OCD subjects with comorbid disorders (Aboujaoude et al., 2009; Sahraian et al., 2017; Stewart et al., 2010) and the remaining studies excluded comorbid patients. Both subgroups exhibited significant reduction in the mean Y-BOCS score, but more favourable results were exhibited in patients without comorbid disorders. The overall mean reduction of Y-BOCS score was 8.16 (95% CI: 0.93–15.38, $p = 0.027$) points in patients with comorbid disorders as compared to 12.74 (95% CI: 8.90–16.58, $p < 0.001$) points in patients

Table 1
Characteristics of included studies.

Study	Methods	Trial duration (weeks)	Participants	Target Dose (mg/day)	SRI-refractory	Comorbid disorders	Minimum Y-BOCS for inclusion	Baseline Y-BOCS Mean(SD)	End-point Y-BOCS Mean(SD)	Y-BOCS reduction criterion for treatment response	Number of treatment responders
Feusner et al. (2009)	Open-label	12	Memantine (10)	20	No	No	≥16	27.6(4.4)	16.4(13.6)	≥35%	7/10
Aboujaoude et al. (2009)	Open-label	12	Memantine (14)	20	Yes (≥1 failed adequate trials of SRI for >12 weeks)	Yes	≥18	27.4(5.0)	22.0(9.2)	≥25%	6/14
Stewart et al. (2010)	Single-blinded case- control	62(37.3) days	Memantine (22) Control (22)	18	No	Yes	Not provided	26.8(5.2)	Not provided	≥25%	Memantine: 8/22
Bakhla et al. (2013)	Open-label	12	Memantine (12)	10	Yes (≥2 failed adequate trials of SRI for >12 weeks)	No	≥25	29.7	19.8	≥25%	8/12
Ghaleiha et al. (2013)	Double-blind placebo-controlled	8	Memantine (19) Placebo (19)	20	No	No	≥21	Memantine: 28.6(5.3) Placebo: 28.7(2.3)	Memantine: 11.5(4.9) Placebo: 18.9(8.8)	≥35%	Memantine: 19/19 Placebo: 6/19
Haghighi et al. (2013)	Double-blind placebo-controlled	12	Memantine (14) Placebo (15)	5–10	No	No	≥21	Memantine: 28.9(4.9) Placebo: 28.1(3.5)	Memantine: 19.6(3.8) Placebo: 23.7(3.6)	≥35%	Memantine: 9/14 Placebo: 0/15
Modarresi et al. (2018)	Double-blind placebo-controlled	12	Memantine (15) Placebo (15)	20	Yes (≥3 failed adequate trials of SRI for >12 weeks)	No	≥24	Memantine 33.9(3.6) Placebo: 33.5(3.3)	Memantine: 20.0(2.6) Placebo: 33.5(3.2)	≥35%	Memantine: 11/15 Placebo: 0/15
Sahraian et al. (2017)	Double-blind placebo-controlled	16	Memantine (19) Placebo (19)	20	No	Yes	≥17	Memantine: 20.3(5.9) Placebo: 22.9(5.7)	Memantine: 9.7(5.4) Placebo: 16.36(4.0)	≥35%	Memantine: 15/19 Placebo: 7/19

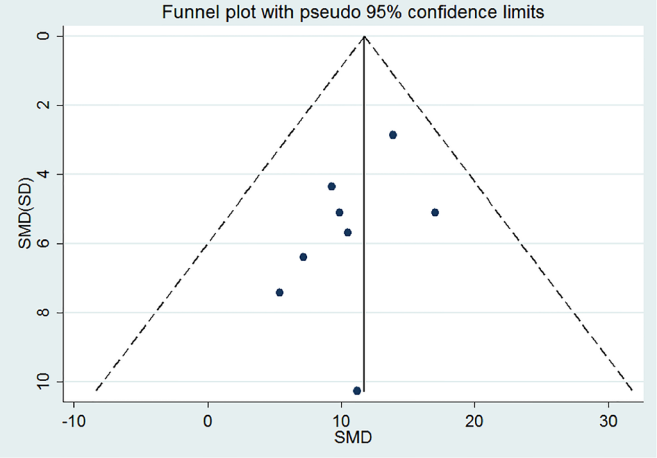

Fig. 1. Funnel plot of memantine treatment for all 8 studies.

with no comorbidity. Fig. 5 shows the Forest plot analysis.

3.3.4. Association of mean reduction of Y-BOCS score with duration of memantine augmentation

Meta-regression analysis was used to test the association of mean Y-BOCS change with duration of memantine intervention. The findings suggested no association between mean reduction of Y-BOCS score and duration of memantine augmentation therapy (beta = −0.11(1.13), $p = 0.426$).

3.4. Secondary outcome measures: meta-analyses of double-blind placebo-controlled studies

Four clinical trials with 135 participants (67 memantine augmentation and 68 placebo) contributed to these analyses:

3.4.1. Mean reduction of Y-BOCS score in memantine versus placebo augmentation groups

The overall mean difference in Y-BOCS score change between memantine and placebo groups was 7.76 (95% CI: 2.58–12.95, $p < 0.001$) points favouring memantine, as shown in Fig. 6. This is equivalent to a further reduction of 27.6% in Y-BOCS for those receiving memantine augmentation.

3.4.2. Proportion of treatment responders in memantine versus placebo augmentation groups

The categorical analysis of responders, defined by a minimum of 35% reduction in Y-BOCS score (Pallanti et al., 2002), in comparison to non-responders indicated that those participants receiving memantine augmentation were 3.61 times more likely to respond to treatment (95% CI: 1.53, 8.53), see Fig. 7. The treatment response was 81% (54 of 67) in the memantine group as compared to 19% (13 of 68) in the placebo group. The number needed to treat (NNT) to benefit from memantine augmentation among moderate to severe OCD patients was 1.47, calculated from the risk difference (RD) analysis.

4. Discussion

This systematic review exhibits that memantine augmentation is an effective treatment intervention for moderate to severe OCD patients. A significant mean reduction of 11.73 points, equivalent to a 39.5% drop, in Y-BOCS ratings was exhibited across eight studies involving 125 OCD subjects receiving memantine augmentation to their first-line pharmacological treatment. The NNT for memantine augmentation is 1.47 when treatment response is defined by a 35% reduction in Y-BOCS ratings. Nearly 8 out of 10 moderate to severe OCD patients exhibited a treatment response to memantine augmentation across the four double-blind placebo-controlled trials, while this was 2 out of 10 for the placebo. This can be clinically important; however the NNT is to be considered with caution due to potential small study effects and publication bias.

Stratification by refractoriness to SRI monotherapy exhibited significant reduction of mean Y-BOCS score in both populations with no evidence of memantine augmentation favouring either of the groups. However, since two studies in the non-refractory subgroup (Ghaleiha et al., 2013; Stewart et al., 2010) did not specifically exclude SRI-refractory patients, it is likely that SRI-refractory subjects might

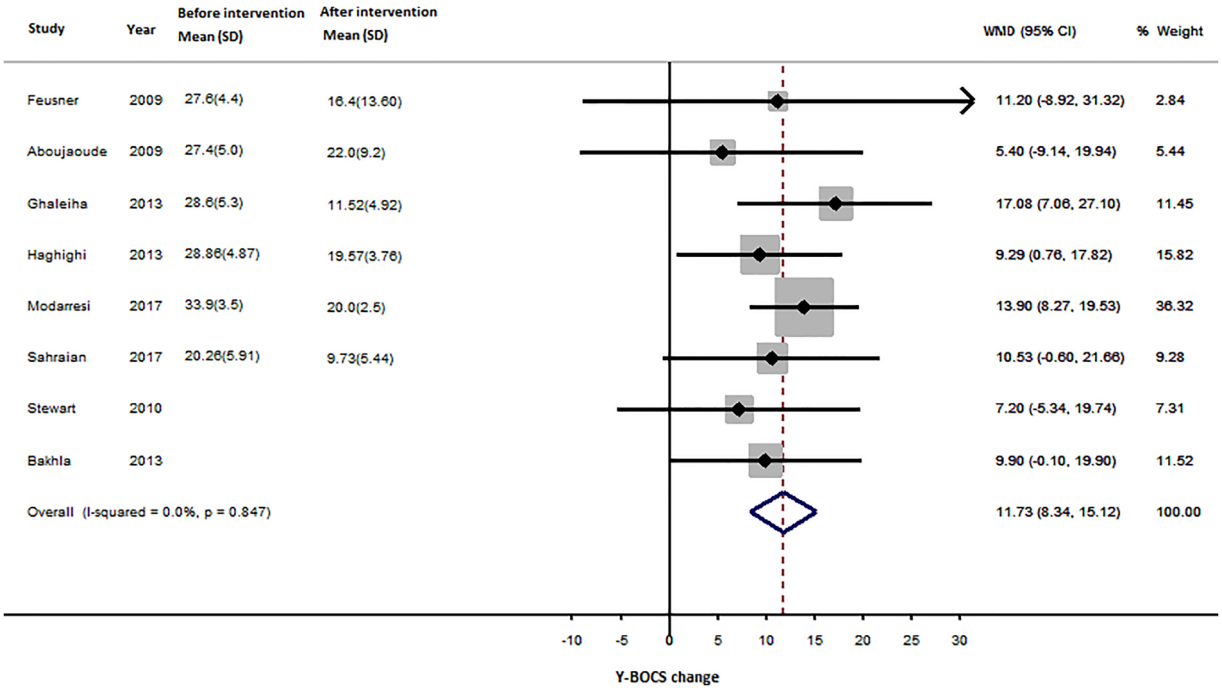

Fig. 2. Meta-analysis of memantine treatment for OCD patients considering 8 studies.

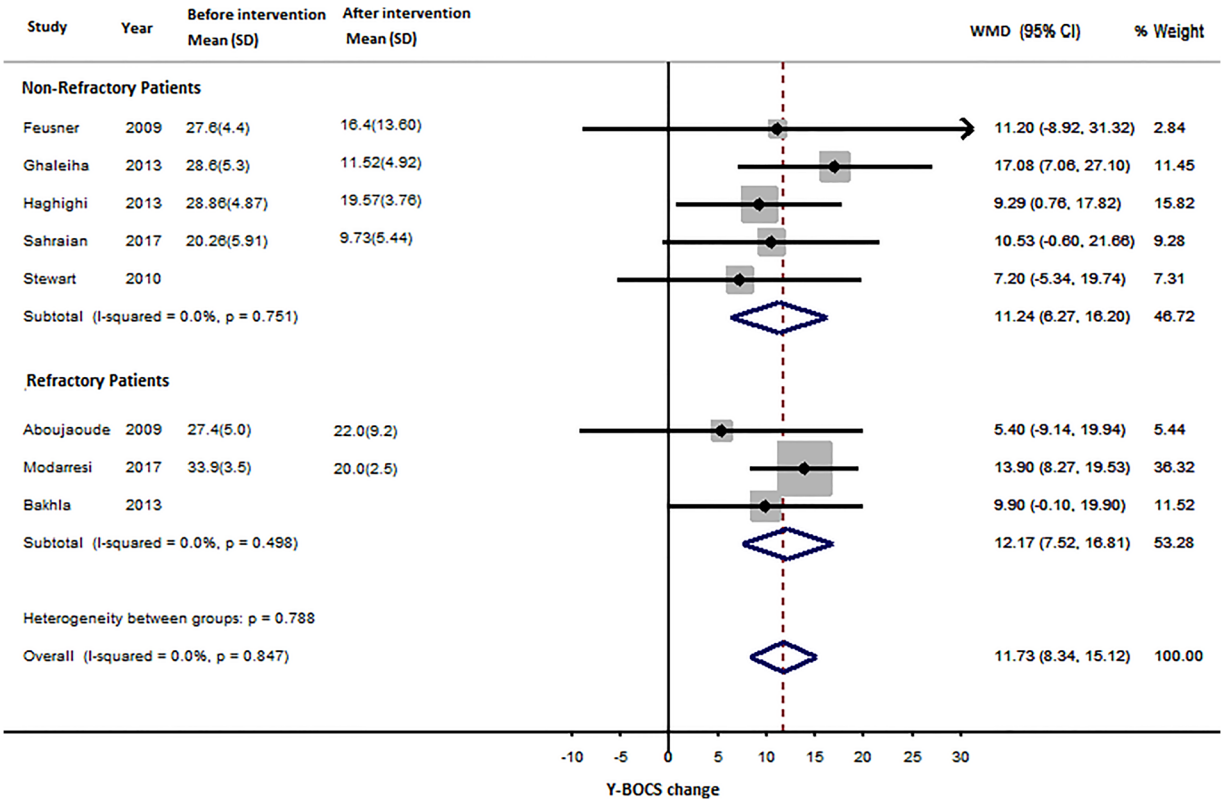

Fig. 3. Investigating the effect of memantine in refractory and non-refractory OCD patients.

have been recruited in those studies, and thus were inevitably included in the non-refractory subgroup in our analysis.

Stratification by the target dose of memantine augmentation exhibited significant reduction of mean Y-BOCS score in both 20 and < 20 mg/day populations, but a more favourable outcome was observed in the 20 mg/day group. Meta-regression exhibited no

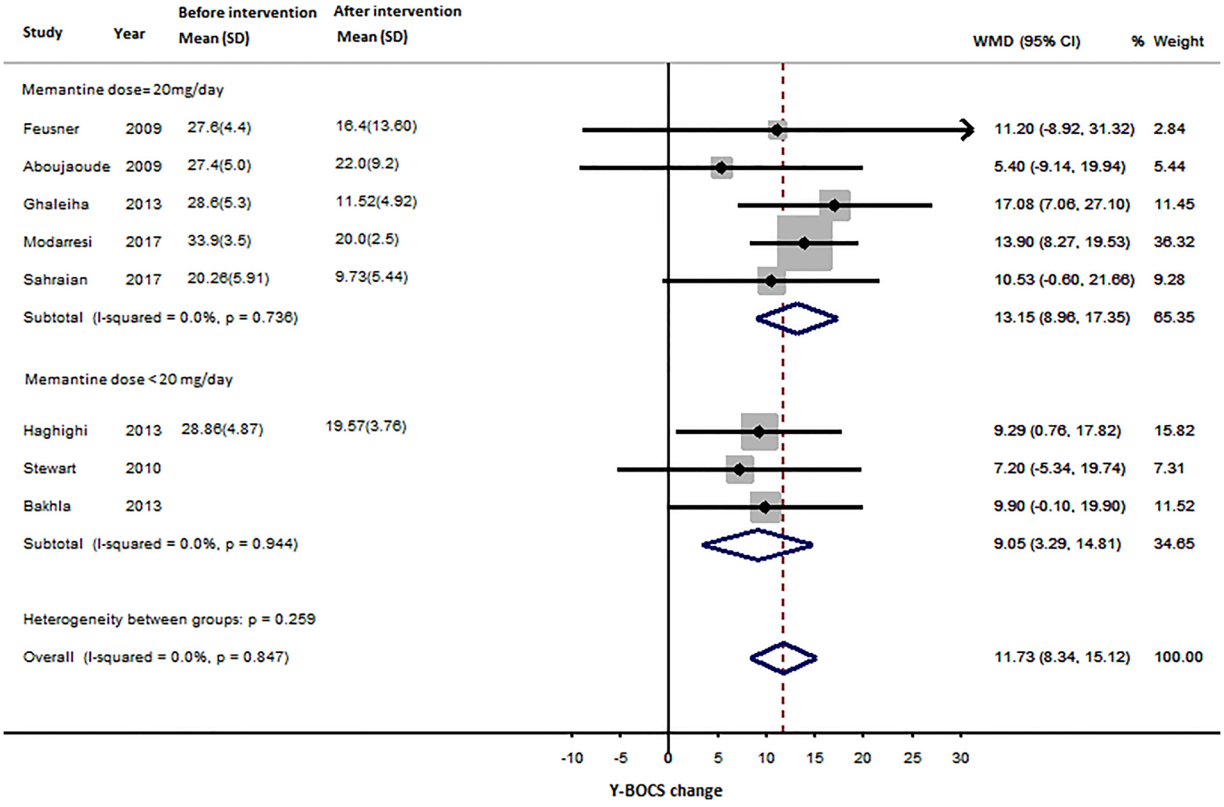

Fig. 4. Investigating the effect of different doses of memantine in treatment of OCD.

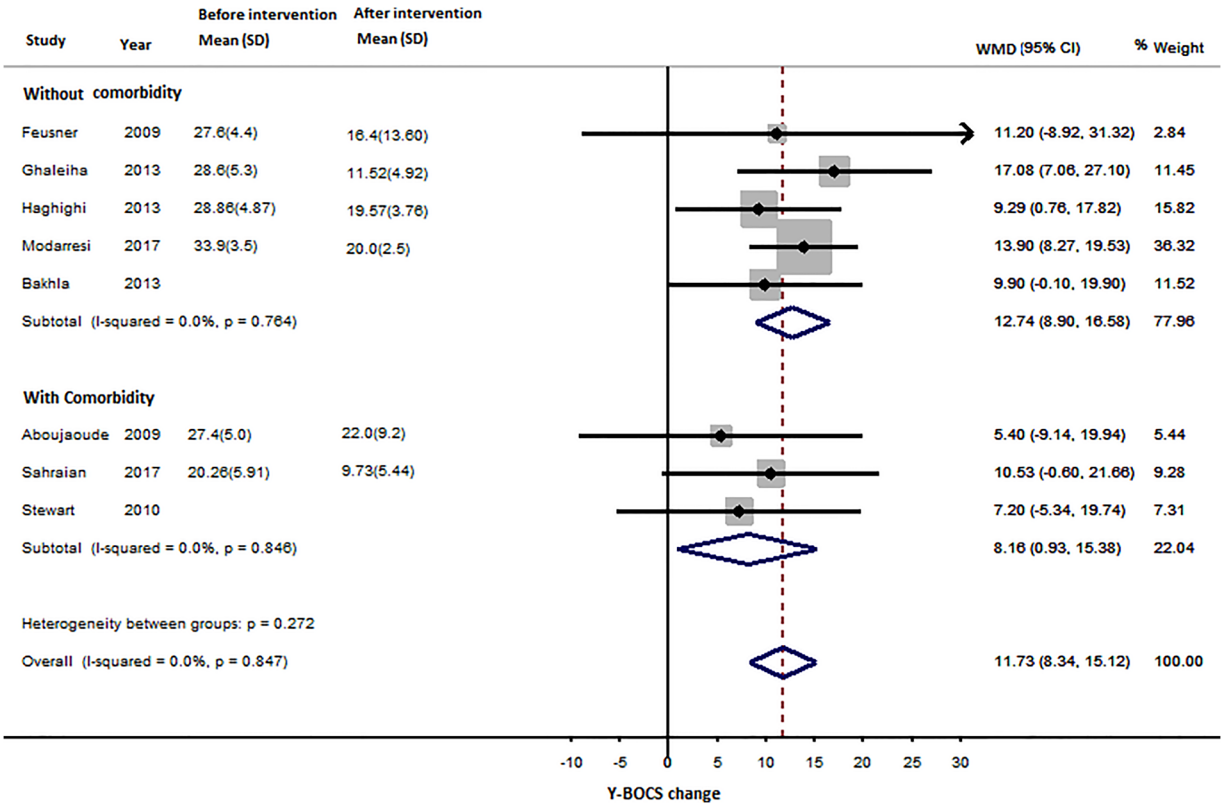

Fig. 5. Investigating the effect of Memantine subdivided by comorbidity.

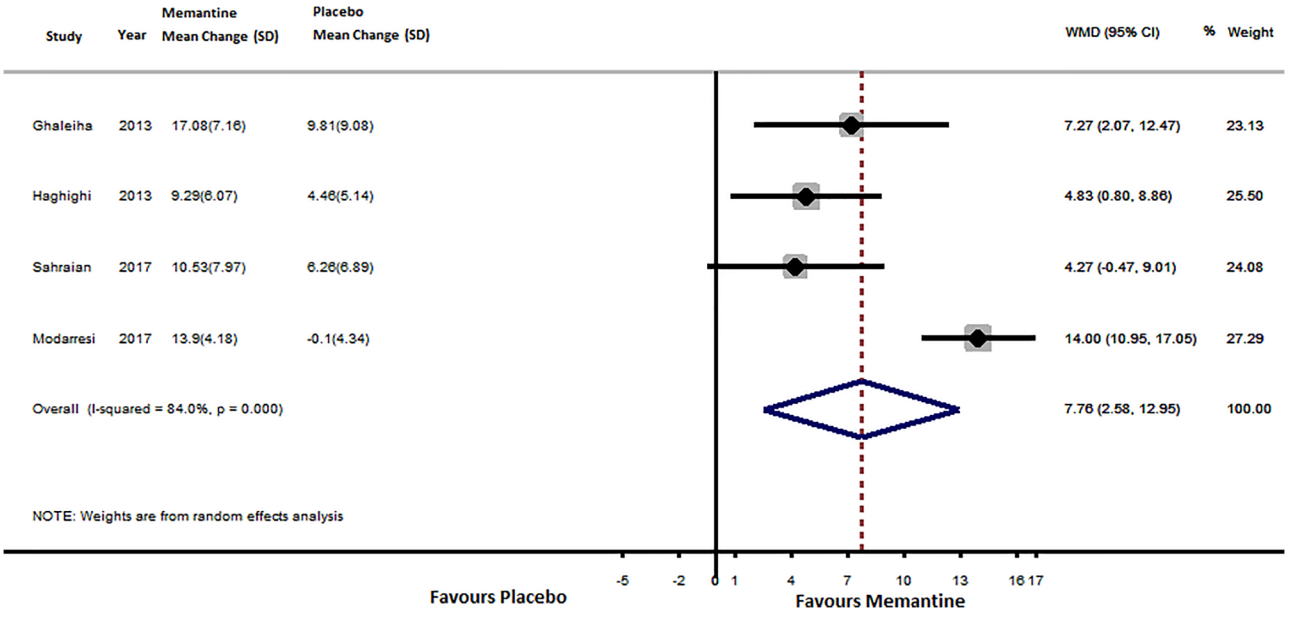

Fig. 6. The mean difference of Y-BOCS score in memantine versus placebo group in OCD patients. The forest plot compares the weighted mean difference (WMD) in memantine and placebo group using random effects model.

association between the mean Y-BOCS change and length of memantine augmentation. These results suggest that a higher dose of memantine should be considered based on tolerability and that patients are less likely to improve if they have not responded after 8 weeks of intervention. However, non-statistically significant relationship in meta-regression does not always correspond to a lack of true relationship (Baker et al., 2009) . In the 12-week trial by Haghighi et al., OCD patients in the memantine group only exhibited statistically significant improvement in Y-BOCS versus the placebo group after 12 weeks of memantine intervention (Haghighi et al., 2013). In the 12-week trial by Modarresi et al., while a time-to-effect of 8 weeks was necessary to observe significant improvement in OCD symptoms, treatment response was only exhibited after 12 weeks of memantine augmentation (Modarresi et al., 2018). We therefore recommend a minimum of 12 weeks for memantine augmentation therapy.

The subgroup of OCD patients with no comorbid disorders appeared to exhibit a more favourable response to memantine augmentation than those with comorbid symptoms. In a systematic review of antipsychotic

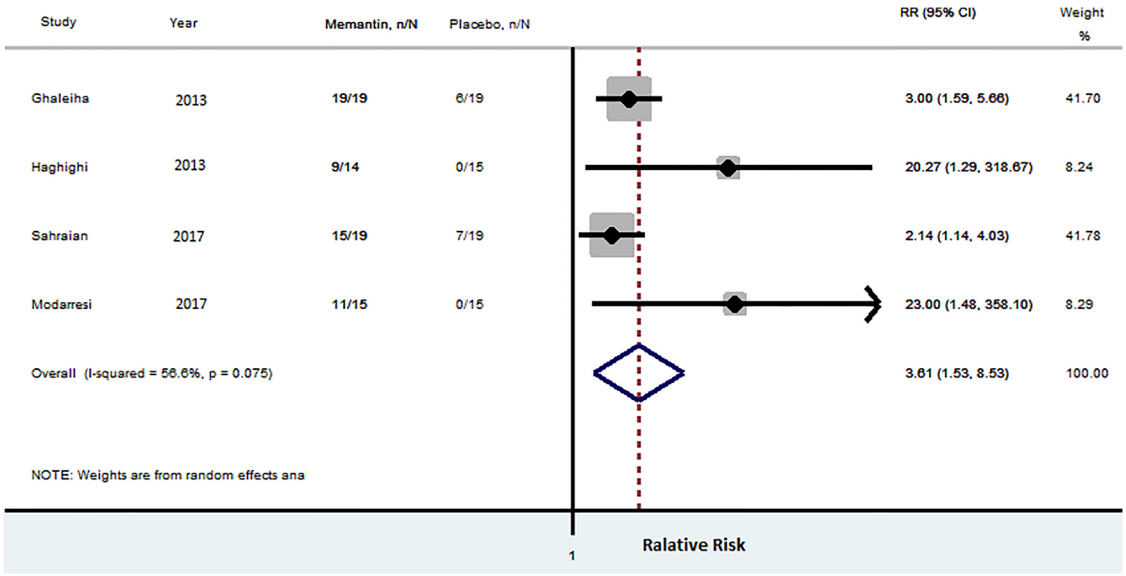

Fig. 7. Relative risk (RR) of response in memantine versus placebo group considering four clinical trials.

augmentation with treatment refractory OCD by Bloch et al., the subgroup of OCD patients with comorbid tics appeared to have a particularly beneficial response to treatment with antipsychotic augmentation (Bloch et al., 2012). This may suggest that antipsychotic augmentation could lead to more favourable results than memantine in OCD patients with comorbid symptoms.

Memantine was generally well tolerated and the reported adverse effects were mild and transient. Two clinical trials reported dropouts because of adverse effects: Haghighi et al. reported one dropout in each of SSRI + memantine and SSRI + placebo groups from adverse effects (Haghighi et al., 2013). Sahraian et al. reported 4 dropouts in the Lithium + Olanzapin + Clonazpam + memantine group and 5 dropouts in the Lithium + Olanzapin + Clonazpam + placebo group from adverse effects (Sahraian et al., 2017). The comparison of side effects between the memantine and placebo groups in double-blind placebo-controlled trials exhibited no statistically significant difference between the two groups. It should be noted that the short follow-up intervals of the studies prevented the assessment of potential long-term adverse effects. All studies with the exception of Modarresi et al. used an upward titration strategy to assess tolerability of patients and reduce risk of adverse effects. The trial by Modarresi et al. used a starting dose of 20 mg/day and found no difference in adverse effects between the memantine and placebo groups (Modarresi et al., 2018).

Given the risk of bias due to small sample sizes and post-randomization exclusions in a number of studies, the interpretation of outcomes from this systematic review should be conducted with caution. All four double-blind placebo-controlled trials considered in this review were conducted by research centers located in Iran and included patients with similar racial background (Ghaleiha et al., 2013; Haghighi et al., 2013; Modarresi et al., 2018; Sahraian et al., 2017). While this can reduce heterogeneity in the meta-analysis, it might also limit the generalization of the outcomes.

Overall, the findings of this systematic review encourage further clinical trials, especially involving larger sample sizes, to establish the efficacy of memantine augmentation in OCD patients. Given the safety and tolerability of memantine, even at higher doses than usually used in clinical practice (Ferguson and Shingleton, 2007), such trials could consider high-dose (≥20 mg/day) memantine augmentation and minimum duration of 12 weeks. A more frequent assessment interval (weekly or two-weekly) is recommended to establish a more accurate time-to-effect.

5. Conclusions

This systematic review combines eight single and double blinded as well as open-label studies involving 215 subjects in the published literature. There was no evidence of publication bias based on the funnel plot of published data. Nevertheless, publication bias in this literature cannot be ruled out, especially because of small sample sizes and postrandomization exclusions. In summary, we found that 20 mg/day memantine augmentation to first-line pharmacological treatment for a period of at least 8 weeks is a safe and effective intervention for moderate to severe OCD.

While SRI is an effective first-line pharmacological treatment, memantine augmentation was shown to further improve moderate to severe OCD symptoms compared to placebo. Memantine augmentation could especially be an attractive intervention in SRI-refractory OCD and OCD patients with manic phase of bipolar disorder who exhibit contraindication to the use of SRI first-line treatment (Sahraian et al., 2017). Given the large body of evidence on the effectiveness of NMDA antagonists in OCD treatment, we anticipate an increased use of glutamate modulating agents such as memantine in clinical interventions.

Declaration of Competing Interest

The authors declare no conflicts of interest to disclose.

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