Clinical and Practical **Psychopharmacology**

Augmentation With Memantine in Obsessive-Compulsive Disorder

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Patients with obsessive-compulsive disorder (OCD) who do not respond adequately to serotonin reuptake inhibitor (SRI) therapy and cognitive behavioral therapy commonly receive SRI augmentation in the form of an atypical antipsychotic drug. Memantine is another augmentation strategy that has been trialed. A recent systematic review and meta-analysis found very large improvements associated with memantine augmentation in OCD. Specifically, in 4 randomized controlled trials (RCTs), the response rate was 81% in 67 memantine-treated patients vs only 19% in 68 placebo-treated patients. The weighted mean difference between memantine and placebo groups was nearly 8 points on the Yale-Brown Obsessive Compulsive Scale. Such striking differences for intervention vs placebo in a difficult-to-treat disorder demand scrutiny. An examination of the RCTs on which the meta-analysis was based showed that all 4 RCTs emerged from the same geographical area, limiting the generalizability of the findings. Of greater concern, all 4 RCTs presented what were effectively completer analyses of data, compromising the scientific validity of the findings. There were several other concerns about the individual studies and about the meta-analysis, itself. Therefore, a reasonable conclusion is that, when the internal and external validity of studies in a meta-analysis are compromised, the findings and conclusions of the meta-analysis cannot be considered sound. It is concluded that, despite the very large benefits reportedly associated with memantine augmentation, the routine use of memantine as an augmentation agent for OCD cannot as yet be recommended.

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Obsessive-compulsive disorder (OCD) is not easy to treat. Whereas serotonin reuptake inhibitor (SRI) drugs are first-line agents for OCD, many patients require SRI augmentation, usually with an atypical antipsychotic drug, in addition to cognitive behavioral therapy. However, antipsychotic drugs are associated with a range of adverse effects. So other augmentation agents have also been studied. Memantine is one such agent that has been examined in uncontrolled and controlled trials. In this connection, Modarresi et al[1] described a systematic review and meta-analysis of memantine augmentation in moderate to severe OCD. They found that memantine augmentation was associated with very large benefits. If their findings are valid, then the approach to the management of OCD could change.

This article therefore presents a critical examination of the meta-analysis[1] and its findings. Readers are also referred to earlier articles in this column on how to critically read a meta-analysis.[2–5]

Meta-Analysis: Memantine Augmentation in Obsessive-Compulsive Disorder

Modarresi et al[1] searched scientific electronic databases, clinical trial registries, and reference lists for trials of the use of memantine as an augmentation agent in adults with moderate to severe OCD. They identified 3 small, open-label, uncontrolled trials; 1 small, single-blind, nonrandomized controlled trial; and 4 small-to-medium, double-blind, randomized controlled trials (RCTs).

The primary outcome was the mean reduction, across trials, in memantine-treated patients, in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score. Memantine augmentation was associated with a very large benefit: the mean improvement after at least 8 weeks of augmentation was 11.7 (95% CI, 8.3–15.1) Y-BOCS points, equivalent to a nearly 40% mean reduction in illness severity. This analysis was based on data from 125 patients in 8 trials. Visual inspection of the funnel plot suggested publication bias.

There were several secondary analyses, such as the examination of outcomes after stratification for SRI refractoriness, after stratification for memantine dose, and after stratification for comorbid symptoms. Meta-regression examined outcomes as a function of treatment duration. The most important analysis, the pooling of data from RCTs, was presented as the final secondary analysis.

There were 4 RCTs[6–9] in which 68 patients received placebo and 67 patients received memantine in the target dose of 5–10 mg/d (1 RCT) or 20 mg/d (3 RCTs) for 8 weeks (1 RCT), 12 weeks (2 RCTs), or 16 weeks (1 RCT). Only 1 of these trials[9] recruited only SRI-refractory patients; 2 trials[7,8] placed no restrictions on prior treatment exposure and response thereto, and 1 trial,[6] in fact, specifically recruited patients who had not received psychotropic medications during the previous 6 weeks. Very unusually, one trial[8] was conducted specifically during the manic phase of bipolar type I disorder.

A random effects meta-analysis of findings from these 4 RCTs showed that memantine augmentation was substantially superior to placebo by a mean of 7.8 (95% CI, 2.6–13.0) Y-BOCS points.

Heterogeneity was high (I^2 = 84%). Treatment response was declared in 54 (81%) of 67 memantine patients as compared with only 13 (19%) of 68 placebo patients. This translates to a number needed to treat (NNT) value of 1.6 (stated as 1.5 by the authors); that is, fewer than 2 patients with moderate to severe OCD must receive memantine augmentation for 1 extra patient to respond.

Critical Comments

Modarresi et al[1] did not present a pooled effect size; nevertheless, the pooled response rate of 81% vs 19% for memantine vs placebo, with a corresponding NNT of 1.6, is so striking that the prudent reader would want to take a closer look at the data. There are two important concerns.

The first concern is obvious, and the authors of the meta-analysis[1] themselves commented on it in their discussion: all 4 RCTs were conducted in Iran. Whereas the authors[1] stated that this limits the generalizability of the findings, there is a deeper issue at stake. During the past 10–15 years, well over a hundred psychopharmacology RCTs have been published from this part of the world. These RCTs have examined a wide range of drugs for a wide range of indications, and despite small sample sizes (such as n = 30), which usually indicates inadequate statistical power, the results of the RCTs have almost always statistically significantly favored the intervention. This is particularly striking when one observes that a substantial number of the RCTs examined unusual rather than conventional interventions for psychiatric disorders. The most parsimonious interpretation of these results, therefore, is that one needs to view them with caution and seek replication from other parts of the world.

The second concern is not at all obvious, and the reader needs to be diligent in examining the RCTs[6–9] on which the meta-analysis[1] was based. To cut a long story short, each RCT presented a completer analysis; that is, they omitted the data of patients who dropped out of treatment. In the Ghaleiha et al[6] RCT, 4 out of 42 patients dropped out; in the Haghighi et al[7] RCT, 11 out of 40 patients dropped out; in the Sahraian et al[8] RCT, 20 out of 58 patients dropped out; and in the Modarresi et al[9] RCT, 2 out of 32 patients dropped out.

As a moderating note to the previous paragraph, in 1 RCT,[8] the authors stated that they performed an "intention-to-treat analysis with at least 1 assessment after the baseline assessment." This effectively eliminated 15 out of 20 dropouts, with the remaining 5 dropouts presumably included in the intent-to-treat sample. Thus, the analysis was very close to a completer analysis. The study, however, was additionally problematic because the authors did not state how missing values were imputed. Furthermore, nowhere in their text and tables did they state the sample sizes on which specific numbers (eg, 4-weekly ratings, response percentages) were based. Therefore, extraction of data for meta-analysis would have involved assumptions based on the CONSORT diagram.

The internal validity of a study is compromised when data from dropouts are ignored in the analysis.[10] So a meta-analysis that is based on compromised data will yield results of questionable validity. In a nutshell, we can no longer confidently consider memantine as a potential augmentation agent in OCD.

Other Comments

Modarresi et al[1] included only those RCTs that recruited patients with a Y-BOCS score of 16 or higher. This excluded the large 8-week RCT (n = 99) of Farnia et al,[11] which recruited patients with Y-BOCS scores of 15 and higher and in which memantine augmentation of fluoxetine was found to be no better than placebo augmentation.

In the Modarresi meta-analysis,[1] the primary outcome was the mean reduction, across all trials, of the Y-BOCS total score in patients who had received memantine. This is an outcome of questionable value because it includes all components of a placebo response, including a true placebo response, regression to the mean, ratings contaminated by Hawthorne and expectancy effects, and other contaminants.[12] The meta-analysis[1] should have restricted itself to the examination of RCT data. In this context, as observed in an earlier article in this column,[13] readers may sometimes need to consider whether the truly relevant clinical outcome is different from that set as the primary outcome by the authors of a meta-analysis.

One RCT[7] stated in its title that it had been conducted in refractory OCD. However, nowhere in the text was this claim substantiated, and, in fact, in the discussion, the authors stated that the patients had suffered from severe OCD "for the first time in their lives" and that they were therefore unclear about whether memantine augmentation might be helpful for "therapy-resistant and refractory OCD."

Finally, one wonders whether the RCT[8] that was conducted during the manic phase of bipolar I disorder belonged in the meta-analysis.[1] In this RCT,[8] memantine was used as an augmentation treatment with lithium, olanzapine, and clonazepam as primary treatments. SRIs were not prescribed. So, if the positive findings of the 4 RCTs[6–9] are valid, a conclusion should be that memantine is effective in OCD regardless of what drug it augments; or, by extension, memantine may benefit OCD in monotherapy!

Take-Home Message

A meta-analysis is only as good as the studies on which it is based. There are concerns about the data and the analyses in all the source RCTs on which the meta-analysis of Modarresi et al[1] was based. Therefore, the findings of this meta-analysis, impressive though they are, cannot guide clinical practice. The case for memantine as an augmentation agent in OCD remains unestablished.

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