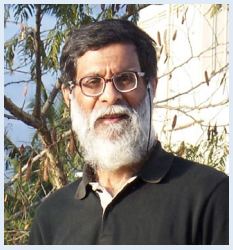
Clinical and Practical **Psychopharmacology**

Memantine as an Augmentation Treatment for Schizophrenia: Limitations of Meta-Analysis for Evidence-Based Evaluation of Research

Chittaranjan Andrade, MD



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.

Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore, India (candrade@psychiatrist.com).

ABSTRACT

The action of memantine on *N*-methyl-D-aspartate (NMDA) glutamatergic receptors and the other pharmacodynamic actions of this drug suggest that it may benefit patients with schizophrenia. Many randomized controlled trials (RCTs) have examined this possibility. These RCTs have been meta-analyzed by at least 2 groups of authors. In one meta-analysis (8 RCTs, pooled N = 448), memantine (20 mg/d for 6–12 weeks) augmentation of antipsychotic drug therapy was found to attenuate the severity of negative symptoms and improve cognitive functioning; in both regards, the effect was large. Memantine was also associated with a small but statistically significant reduction in general psychopathology. Whereas memantine did not significantly attenuate positive symptom, depression, total psychopathology, and global illness ratings, it was also not associated with an increased risk of individual adverse events, discontinuation due to adverse events, or all-cause discontinuation. The findings of the other meta-analysis, which examined much the same body of literature, were largely similar. On the surface, these results suggest that memantine may be considered for the reduction of negative symptoms and cognitive impairment in schizophrenia. However, an examination of the individual RCTs and a careful look at the findings of the meta-analyses identify so many important concerns that it is probably premature to draw conclusions about the usefulness of memantine as an augmentation strategy in schizophrenia. At best, it may be stated that there is a signal that supports the study of memantine in schizophrenia patients who are specifically impaired by negative symptoms and cognitive complaints. This is a good example of a situation in which meta-analysis did not provide a trustable evidence-based interpretation of literature.

J Clin Psychiatry 2017;78(9):e1307–e1309
https://doi.org/10.4088/JCP.17f11998

Introduction

Many patients with schizophrenia do not respond completely to treatment with antipsychotic medications and continue to experience positive symptoms, negative symptoms, mood disturbance, cognitive impairment, and other difficulties. A wide range of pharmaceutical agents has been trialed as augmentation therapy for such patients; these agents include antidepressants, anticonvulsants, antihistaminics, antihypertensives, anti-inflammatory drugs, benzodiazepines, β-blockers, cannabis derivatives, cholinesterase inhibitors, glutamatergic agents, hormones such as oxytocin and erythropoietin, mood stabilizers, neuropeptides, omega-3 fatty acids, serotonin 5-HT_3 and 5-HT_6 receptor antagonists, sigma receptor ligands, statins, and xanthine oxidase inhibitors, among many others. Memantine is one among these.

Why Memantine?

Memantine is a low affinity, fast-off, voltage-dependent, noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist that has been approved for the treatment of moderate to severe Alzheimer's disease.[1] Speculatively, there are at least 4 reasons why memantine may benefit patients with schizophrenia:

1. Glutamatergic excitotoxicity has been suggested as a pathological mechanism in schizophrenia, particularly in early schizophrenia, and as an explanation for positive symptoms and neuroanatomical changes.[2,3] Memantine interferes little with physiological glutamatergic signaling but inhibits the mechanisms underlying glutamate-driven neuronal excitotoxicity.[4]
2. Memantine has an inhibitory effect on the 5-HT_3 receptor,[5] and 5-HT_3 antagonists have been suggested to improve negative symptoms in schizophrenia.[6]
3. Memantine has complex actions on α4β2, α7, and other nicotinic cholinergic receptors,[7] and these actions may be relevant for the attenuation of cognitive deficits in schizophrenia.
4. Memantine may have D_2 receptor agonistic effects[8]; whereas this could be of concern for positive symptoms of schizophrenia, it may contribute to the attenuation of negative symptoms.

These speculations could support the consideration of memantine to treat the positive, negative, and/or cognitive symptoms of schizophrenia.

Memantine for Schizophrenia: Clinical Evidence

No matter how elegant pharmacodynamic speculations are, they remain speculations until supported by clinical evidence. In this context, Kishi et al[9] described a systematic review and meta-analysis of the clinical benefits of memantine augmentation of antipsychotic drugs in patients with schizophrenia.

These authors[9] searched electronic databases, clinical trial registries, reference lists, and other sources and identified 8 randomized, double-blind, placebo-controlled trials (pooled N = 448) that met their study selection criteria. One study was a crossover trial; in this study, only data from the first treatment phase were examined because a crossover effect was identified despite a 2-week washout period.

These randomized controlled trials (RCTs) were 6–12 (median, 12) weeks in duration. Patients in the studies were young (mean, 39 years). Risperidone and clozapine were the augmented antipsychotic drugs in 2 studies each. One study augmented only first-generation antipsychotic drugs, 1 study augmented olanzapine, and the remaining 2 studies augmented a mixture of second-generation antipsychotic drugs. All studies dosed memantine augmentation therapy at 20 mg/d.

Important findings from this meta-analysis[9] are presented in Table 1. In summary, memantine was associated with significant improvement in negative symptoms, cognition, and general psychopathology, but not in depression, total psychopathology, or global ratings of illness severity. The magnitude of improvement was large for both negative symptoms and cognition. The magnitude of improvement in general psychopathology was clinically negligible. Memantine was not associated with an increased risk of specific adverse events or of dropout due to adverse events. There did not appear to be evidence of publication bias.

In meta-regression, younger age was associated with better negative symptom outcomes, but this could have been a false-positive error arising from the many relationships tested, and anyway the number of RCTs was too small for the meta-regression results to be confidently interpreted.

Table 1. Important Findings From a Meta-Analysis of RCTs of Memantine (20 mg/d) vs Placebo Augmentation in Antipsychotic-Treated Schizophrenia[a]

1. Memantine was superior to placebo for the attenuation of negative symptom ratings (7 RCTs; N = 367; SMD, 0.96; 95% CI, 0.27–1.64). There was substantial heterogeneity (I^2 = 88%).
2. Memantine was superior to placebo for the attenuation of general psychopathology ratings (4 RCTs; N = 151; MD, 1.62; 95% CI, 0.59–2.65. There was no heterogeneity (I^2 = 0%).
3. Memantine was superior to placebo for the increase in MMSE scores (3 RCTs; N = 83; MD, 3.07; 95% CI, 1.69–4.46). There was little heterogeneity (I^2 = 21%).
4. Memantine was not superior to placebo for the attenuation of positive symptom ratings (7 RCTs; N = 367; SMD, 0.46; 95% CI, −0.05 to 0.96). There was substantial heterogeneity (I^2 = 80%).
5. Memantine was not superior to placebo for the attenuation of total psychopathology ratings (5 RCTs; N = 271; SMD, 0.75; 95% CI, −0.03 to 1.52). There was substantial heterogeneity (I^2 = 86%).
6. On other efficacy outcomes, memantine was not superior to placebo for the attenuation of depression (4 RCTs; N = 201; SMD, 0.13) and of global ratings of illness severity (4 RCTs; N = 226; SMD, 0.19). There were no dropouts due to inefficacy.
7. Memantine was not associated with a higher risk of all-cause discontinuation or discontinuation due to adverse effects. Memantine was not associated with an increased risk of serious adverse events or of specific adverse events such as fatigue, dizziness, headache, nausea, and constipation.

[a]Data from Kishi et al.[9]
Abbreviations: CI = confidence interval, MD = mean difference, MMSE = Mini-Mental State Examination, RCT = randomized controlled trial, SMD = standardized mean difference.

A Second Meta-Analysis

During the same year, Zheng et al[10] also presented a systematic review and meta-analysis of RCTs of memantine augmentation of antipsychotic drugs in patients with schizophrenia. Seven of the 8 RCTs in this meta-analysis were the same as those in the meta-analysis by Kishi et al.[9] This meta-analysis[10] had 1 Chinese RCT in place of 1 Iranian RCT in the previously described meta-analysis.[9]

The second meta-analysis[10] found memantine superior to placebo for negative symptom ratings and Mini-Mental State Examination (MMSE) scores but not for general psychopathology ratings. Other outcomes were largely the same as in the previously described meta-analysis.[9]

Concerns About the Primary Data

There are potential biasing influences in the primary data in the meta-analysis that was described in detail[9]; most of these concerns apply to the other meta-analysis,[10] as well. One RCT, from Brazil, randomized just 22 patients and obtained a standardized mean difference (SMD) of 3.33, favoring memantine over placebo for negative symptom outcomes. This effect size is so large as to be incredible in parallel-group, clinical trial research.

Four of the 8 RCTs were from a single country (Iran), and all 4 found memantine superior to placebo on at least some efficacy outcomes. In contrast, only 2 of the remaining 4 RCTs from other countries showed an efficacy advantage for memantine. With specific reference to the negative symptom data, the SMDs for the 3 Iranian RCTs (that were included in the analysis) were very large and lay in the 1.1 to 1.6 range; that of the Brazilian RCT, as already mentioned, was astronomically large at 3.33; and those of the remaining 3 RCTs lay in the near null, 0.01 to 0.05 range. The discrepancies are substantial and striking.

Memantine was superior to placebo for 3 outcomes: negative symptoms ratings (7 RCTs), MMSE scores (3 RCTs), and general psychopathology ratings (4 RCTs). One RCT in each of these 3 analyses provided observed cases data instead of intent-to-treat data. This RCT was associated with significant and large effect sizes for both negative symptom and MMSE outcomes. The scope for bias in the analyses is therefore large.

The advantage for memantine for general psychopathology ratings was driven by a single, small (N = 40) RCT with 90% weightage in the analysis. The high weightage appeared to be because of the precision of the findings in the study. The other 3 RCTs had large confidence intervals that were

roughly equally spread across the null line. The validity of this analysis is therefore uncertain.

Although memantine was superior to placebo for MMSE outcomes, this result is hard to interpret because the MMSE is not an appropriate instrument for the measurement of cognitive dysfunction in schizophrenia.

Seven of the 8 RCTs had a sample size in the 22 to 64 (median, 40) subjects range. These were all industry-independent. Six of these had outcomes that favored memantine. The only industry-driven RCT was large (N = 138), and no outcome favored memantine. This is an unusual reversal of what is often seen—that small studies fail to find a statistically significant effect (unless there is evidence of publication bias) and that large, industry-driven studies find a significant effect favoring the study medication.

Heterogeneity in most analyses was so large as to render the findings hard to interpret. Sensitivity analyses did suggest sources of heterogeneity, but these were based on too few RCTs, or the outcomes were insufficiently logical for confident conclusions to be drawn. As an example, in the negative symptom analysis, there was no heterogeneity ($I^2 = 0\%$) in 2 risperidone RCTs and substantial heterogeneity ($I^2 = 90\%$) in the remaining 5 RCTs. Two RCTs is too small a number to allow a conclusion that memantine effectively attenuates negative symptoms in risperidone-treated patients, and if this were a true finding, it would beg the question of what is special about the risperidone-memantine interaction.

One study was conducted in patients with negative symptoms; a few in patients with residual positive symptoms or refractory schizophrenia; and a few in unselected patients with schizophrenia. Furthermore, different studies were conducted with different objectives; reduction in negative symptoms, improvement in cognition, and reduction in total psychopathology were all primary objectives in different studies. Therefore, it is difficult to conclude to what kind of schizophrenia patient the results of the meta-analysis can be generalized.

Summary

On the surface, the findings of meta-analysis appear to suggest that the average antipsychotic-treated patient with schizophrenia can expect to experience a substantial reduction in negative symptoms, a substantial improvement in cognition, and a small improvement in general psychopathology after receiving augmentation treatment with memantine (20 mg/d) for 6–12 weeks. However, there are far too many concerns about the RCTs that were the source material for the meta-analysis, and far too many concerns in the findings of the meta-analysis, for confident clinical guidance to be possible. At best, it is suggested that there is a signal to encourage the study of memantine in schizophrenia patients who have persistent negative symptoms and/or clinically significant cognitive impairment. This conclusion could have been drawn from an inspection of the results of the original RCTs. Meta-analysis has not contributed to a better understanding of the literature in the field.

Published online: November 21, 2017.

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