Clinical and Practical **Psychopharmacology**

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The Use of Statins for Antipsychotic Augmentation in Schizophrenia: Examination of Meta-Analyses With Flawed Methods and Conclusions

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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

A very large number of psychopharmacologic agents have been trialed as antipsychotic augmentation strategies for the improvement of positive, negative, mood, cognitive, and other symptoms of schizophrenia; statins are one among these. Two very recent meta-analyses examined data on statin augmentation from 5 to 6 randomized controlled trials (RCTs) in the field. One meta-analysis found that statins were superior to placebo for the improvement of total scale and general psychopathology subscale scores on the Positive and Negative Syndrome Scale; statins were no better than placebo for positive and negative subscale outcomes. The other meta-analysis, in contrast, found that statins were superior to placebo for the improvement of positive and negative subscale scores but were no better than placebo for total scale and general psychopathology subscale outcomes. Both meta-analyses were associated with serious flaws such as the combination of studies conducted in contrasting stages of illness, the combination of change and endpoint scores in the same analysis, and the use of numbers that were prima facie incorrect. The first take-home message is that clinicians who read meta-analyses for guidance on how to better treat patients and researchers who read meta-analyses with a view to citing these in their papers both need to exercise due diligence to determine whether what they are reading is valid or flawed. Because this could be a difficult task, journal editors and reviewers need to take more care during manuscript screening and processing than they appear to be doing at present. The second take-home message is that the consideration of statin augmentation is based on very few RCTs and the differences between trial drug and placebo in these RCTs are mostly so small as to be clinically not worth considering.

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About 10%–45% of patients with schizophrenia are treatment resistant.[1] These patients are usually considered for additional psychopharmacologic or brain stimulation interventions with targets being positive symptoms, negative symptoms, mood disturbance, cognitive impairment, and behavioral disturbances or limitations. Antipsychotic augmentation interventions that have been studied in such patients 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, xanthine oxidase inhibitors, and others.[2–5]

Statins and Schizophrenia

The metabolic syndrome is common in schizophrenia,[6] and, therefore, statins may be reasonably considered for primary prevention in schizophrenia patients at risk of cardiovascular disease events.[7] Interestingly, statins have also been studied in randomized controlled trials (RCTs) as augmentation treatments in resistant schizophrenia.

Many mechanisms have been proposed to explain possible statin benefits in the central nervous system.[8] A tempting hypothesis is that, because inflammatory mechanisms may play a role in the pathophysiology of schizophrenia[9–12] and because statins may have anti-inflammatory properties,[13,14] the statins that cross the blood-brain barrier may favorably address disease processes in schizophrenia in a manner that is different from that by antipsychotic drugs. In this context, nonsteroidal anti-inflammatory drugs have also been trialed in schizophrenia, though with unimpressive effects.[15,16]

Two meta-analyses,[17,18] published earlier this year, examined whether statins usefully augment antipsychotic drugs in patients with schizophrenia. Whereas the meta-analyses examined much the same body of literature, they extracted and analyzed the data differently and obtained different results.

The present article examines the two meta-analyses[17,18] with the following objectives:

1. To draw clinically useful conclusions about the possible role of statins as antipsychotic augmentation agents.
2. To warn readers that many published meta-analyses have serious shortcomings and may not present trustworthy results.

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Nomura et al: Methods and Results

These authors[17] searched electronic databases, reference lists, and other sources for RCTs on the use of statins in schizophrenia. They identified 5 RCTs that investigated atorvastatin, lovastatin, pravastatin, and simvastatin. The pooled sample included 236 patients. The trials were 6–12 weeks in duration. Three trials had been conducted in Iran, 1 in Pakistan, and 1 in the United States.

The primary outcome was improvement in Positive and Negative Syndrome Scale (PANSS) scores. In the pooled analysis of 4 RCTs (N = 174), the authors found that statins outperformed placebo on the primary outcome. The mean difference (MD) was 1.96 (95% confidence interval [CI], 0.98–2.94). There was no heterogeneity in the analysis.

The advantage for statins for improvement in general psychopathology subscale scores was on the threshold of significance (MD, 0.40; 95% CI, 0.00–0.81). Improvements in PANSS positive and negative subscales were not significantly different between groups. Discontinuation due to treatment inefficacy and all cause discontinuation also did not differ between groups.

Nomura et al: Concerns

Results obtained from the study of samples are intended to be generalized to the population from which the samples were drawn. In their pooled analysis of the primary outcome, Nomura et al[17] included one RCT[19] of patients whose mean baseline PANSS score was approximately 127; they also included an RCT[20] of patients whose mean baseline PANSS score was approximately 47. An examination of the original RCTs showed that the former study had been conducted in acutely ill patients with predominantly positive symptoms whereas the latter study had been conducted in chronically ill patients with predominantly negative symptoms. So to what population should the results of this meta-analysis be generalized?

Nomura et al[17] concluded in their abstract that "statins may have considerable potential as an add-on therapy for schizophrenia." This enthusiastic endorsement is unjustified, especially when made in the abstract, which is the only part of the paper that most readers look at and perhaps the only part of the paper that some authors look at when they cite references.[21] The reason why the conclusion is not justified is that PANSS scores can lie in the range of 30–210; in most clinical trials, the range is 60–120. So a mean difference of 1.96 points is actually a negligible advantage for statins over placebo. Expressed otherwise, the difference is too small to be clinically discernible.

More concerning were the serious errors in the analysis itself. In their meta-analysis of the primary outcome, the authors used improvement scores for some studies (eg, Ghanizadeh et al[19]) and endpoint scores for other studies (eg, Vincenzi et al[22]). This is simply unacceptable. Improvement scores and endpoint scores are different outcomes and will have different variances, so it is statistically incorrect as well as conceptually meaningless to pool these different outcomes in meta-analysis. Other problems also characterized the paper, such as the use of meta-regression analysis with so few RCTs.

Shen et al: Methods and Results

These authors[18] identified 6 RCTs: 1 RCT with 131 patients in addition to the 5 RCTs identified in the previous meta-analysis. In this second meta-analysis, pooled statins did not differ from placebo for PANSS total scores or for PANSS general psychopathology subscale scores. However, statins were associated with a small but statistically significant advantage over placebo for PANSS positive subscale scores (standardized mean difference [SMD], 0.31; 95% CI, 0.01–0.62) and for PANSS negative subscale scores (SMD, 0.31; 95% CI, 0.10–0.53).

Shen et al: Concerns

Some concerns about the Shen et al[18] meta-analysis are the same as those about the Nomura et al[17] meta-analysis. For example, Shen et al also combined data from studies of patients in starkly contrasting phases of illness and they also combined change scores with endpoint scores in the same analysis; the change scores are seen as values with a negative sign in the forest plots. In fact, in their Methods section, the authors explicitly stated that "final scores of psychiatric symptoms were used if the follow-up scores were available" and that "changed [*sic*] scores were combined in the same analysis."

There were other problems, too, with this meta-analysis. One is that in one included RCT,[20] change scores were presented as endpoint scores, that is, without a negative sign. This can be deduced from the numbers shown in the forest plot for the PANSS total score; the values are 31.9 for placebo and 14.0 for statins, both being implausible given that the minimum value for PANSS total is 30. Another problem is that for the same RCT[20] the PANSS subscale scores across forest plots did not add up to the PANSS total scale scores in both statin and placebo groups. This means that at least some part of the analysis is invalid because of data errors.

A further problem is that 2 studies were closely similar, and their authorship was also closely similar; they were also published at the same time. It is very likely that one study[23] was a subset of the other,[24] but this cannot be verified because the study with the larger numbers was published only as an abstract. Shen et al[18] did not consider this possibility. A final problem is that Shen et al[18] conducted a large number of exploratory meta-analyses, such as examining outcomes for the total scale and each subscale at several different time points, with specific statins, and for different antipsychotic medications. Type I errors occur in such data mining exercises. Other, minor, problems also characterized the paper.

General Comments

The identification of the errors in the meta-analyses,[17,18] as listed in this article, requires a good understanding of meta-analysis as well as a willingness to undertake the onerous job of inspecting the original data in the RCTs that were included

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in the meta-analyses. If the reviewers of the manuscripts missed the flaws, how likely is it that the flaws will be picked up by readers who use meta-analysis to guide their practice, or by authors who intend to cite these meta-analyses in their own papers? Persons who undertake meta-analysis should show greater responsibility in their methods, and journal review processes need to improve considerably.

Clinical Impressions

Upon eyeballing the data from the original RCTs, it appears that there is little meaningful difference between statin and placebo groups in the outcomes reported. This statement is an opinion and is not a statistical conclusion. However, it would take a bold clinician or researcher to find leads worth pursuing in the published RCTs.

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