Antipsychotics in Treatment-Resistant Schizophrenia

Up to one-third of patients with schizophrenia have persistent psychotic symptoms despite adequate antipsychotic treatment. Clozapine is considered the “gold standard” treatment for treatment-resistant schizophrenia, and its introduction into clinical care in the US stemmed from a seminal paper in 1988 by Kane and colleagues, which found evidence for the superior efficacy of clozapine over chlorpromazine in this patient population. However, an increasing number of randomized controlled trials (RCTs) of other antipsychotics in treatment-resistant schizophrenia have been completed.

To integrate evidence on antipsychotics used for treatment-resistant schizophrenia, Samara and colleagues performed a network (also termed multiple-treatments) meta-analysis of RCTs in this patient population. Network meta-analysis facilitates comparison of the relative effectiveness of 2 antipsychotics, even if they have not been directly compared in a trial, through indirect comparisons with 1 or more intermediate comparators. The investigators identified 40 single- or double-blind RCTs, comprising 5172 patients (mean age 39, 72% male) for the meta-analysis. The primary outcome was efficacy, defined as the overall change in symptoms. Other secondary outcome measures included change in positive and negative symptoms, response to treatment, patient dropouts (both for inefficacy as well as for any reason), and adverse events.

For the primary outcome, the researchers found that clozapine was more effective than haloperidol and sertindole; olanzapine was more effective than quetiapine, haloperidol, and sertindole; and risperidone was more effective than sertindole. The researchers reported a pattern of superiority for clozapine, olanzapine, and risperidone for other outcomes, but results were inconsistent and effect sizes were small. “The most surprising finding was that clozapine was not significantly better than most other drugs,” although the researchers noted that few studies were available for antipsychotics other than clozapine, olanzapine, risperidone, and haloperidol. The researchers concluded that insufficient evidence exists in blinded RCTs to determine the most efficacious antipsychotic for treatment-resistant schizophrenia, and that there is a need for future studies with higher doses of clozapine and in patients with extremely treatment-refractory schizophrenia.

In an accompanying editorial, John Kane and Christoph Correll noted that the study findings are in opposition to another network meta-analysis of antipsychotic efficacy in non-refractory schizophrenia.
schizophrenia, which found clozapine to be significantly superior to all other antipsychotics. They also identified the lack of a universal definition of treatment-resistant schizophrenia, clozapine dose, effects of prior antipsychotic treatment, and challenges of blinding clozapine treatment as important factors in interpreting study findings.

The bottom line
Collaboration is needed to perform large trials to resolve uncertainty regarding the most efficacious antipsychotic for treatment-resistant schizophrenia, given the tremendous burden of illness for affected patients and their families.

Disclosures:
Dr Miller is Associate Professor in the Department of Psychiatry at Georgia Regents University in Augusta, GA, and Schizophrenia Section Editor for Psychiatric Times. He reports no conflicts of interest concerning the subject matter of this article.

References:

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