The Role of Clozapine in Treatment-Resistant Schizophrenia

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In this issue of *JAMA Psychiatry*, the study by Samara et al[1] provides an important update on the evidence surrounding clozapine as the treatment of choice for those individuals with schizophrenia that is considered resistant to other medications. The authors indicate that as many as one-third of patients with schizophrenia experience persistent psychotic symptoms despite adequate treatment with antipsychotics. Therefore, the management of schizophrenia in these patients represents a major public health challenge in human and economic terms.

Many guidelines promulgated by national agencies and professional societies recommend clozapine when other drugs fail, and clozapine remains the only medication with regulatory approval for patients with treatment-refractory schizophrenia (and for reducing suicidal behavior). The meta-analysis by Samara and colleagues[1] questions the unique role of clozapine for patients who have not responded to other antipsychotics by concluding that few blinded data support clozapine's superiority over olanzapine and risperidone in this patient population.

Although we will discuss potential problems and pitfalls in conducting such analyses and the studies on which they are based, our first reaction is how unfortunate it is that our field still struggles with this question more than 25 years after the 1988 publication by Kane et al[2] led to the introduction of clozapine into clinical care in the United States. Given the number of people affected and the profound effect of treatment resistance on the lives of hundreds of thousands of patients and families around the world, this struggle seems unconscionable. The issue now is not to fix the blame but to find a solution. A necessary step to achieve this solution would involve the collaboration of industry, academia, and federal agencies to design, fund, and conduct studies to resolve this uncertainty, a need implied by the authors.

How firm are the authors' conclusions? In our view, they have done an excellent job of analyzing available data and exploring the potential mediators, moderators, and possible confounds in this context. Some of the subgroup and post hoc sensitivity analyses suffer from low statistical power, as the authors acknowledge. Areas of particular importance would be definitions of treatment refractoriness, the risk for attrition and/or reporting bias, the antipsychotic dose, the effect of prior antipsychotic treatment, and the difficulty of blinding clozapine treatment assignment.

No universally accepted or applied criteria exist for treatment refractoriness, and considerable heterogeneity remains in this domain. The criteria applied 28 years ago[2] might have

been far more stringent than those in many more recent studies. The extent to which treatment refractoriness is documented prospectively is another concern, as is the manner in which clinical trials have been conducted in recent years, with considerable potential enrollment bias and higher and higher degrees of placebo response (which can have an impact, even in studies of patients purported to have refractory disease).

The dosage issue is potentially very important because clozapine is the only antipsychotic for which reasonably consistent correlations between plasma levels and clinical response have been reported, although universal agreement on what the threshold should be is lacking. In general, data suggest that the mean clozapine dose of 392 mg/d reported in the comparisons with other second-generation antipsychotics might not be as adequate as the 511 mg/d reported in those studies involving first-generation comparators. The metaregression analysis using antipsychotic dose was, as the authors suggest, markedly weak.

Moreover, in recent years, clozapine-treated patients might have experienced treatment failure with risperidone or olanzapine, whereas patients randomized to those antipsychotics probably had not undergone prior failed trials of these drugs because previous failure would have been an exclusion criterion. Furthermore, although functional unblinding of clozapine treatment owing to its unique adverse effects, such as hypersalivation, might have biased results in favor of clozapine, the aim in more recent studies was often to show comparable efficacy of other second-generation antipsychotics vs clozapine, which also could have attenuated the efficacy signal for clozapine.

Given these complexities and caveats, we are concerned that the results of this state-of-the-art meta-analysis will be confusing to clinicians, patients, and families. First, these findings are in direct opposition to those of a recent meta-analysis of antipsychotic efficacy in the short-term treatment of patients with nonrefractory schizophrenia conducted by Leucht et al.[3] In that meta-analysis, which also used the multiple-treatment meta-analytic approach of ranking antipsychotics by using not only direct but also indirect comparisons via common comparators, clozapine was significantly superior to all other antipsychotics, including risperidone and olanzapine.[3] Second, there is a general view that clozapine is, if anything, underused in clinical care. This notion comes from an abundance of cohort and mirror-image studies that have consistently documented strong, clinically relevant efficacy and effectiveness of clozapine in patients who did not respond to other antipsychotics. For example, in an open algorithm-based study, patients with first-episode schizophrenia received 2 successive treatment trials with risperidone or olanzapine for 12 weeks and switched to the other medication in case of nonresponse

after 12 weeks.[4] Each trial consisted of low-, full-, or high-dose treatment lasting up to 4 weeks each, with dose adjustments according to response or tolerability. In the first trial, 74.5% of individuals responded to risperidone or olanzapine. However, in nonresponders, a switch to the other antipsychotic resulted in a response rate of 16.6% combined across risperidone and olanzapine. Remarkably, when patients received clozapine as the third trial drug, the response rate was 75.0%, similar to that of the first trial.[4]

Nevertheless, in contrast to the studies included in the meta-analysis by Samara and colleagues,[1] those showing superiority of clozapine, including randomized clinical trials (RCTs),[5] were all open-label studies. Whereas the blinded, randomized studies failed to show a difference between clozapine and other second-generation antipsychotics in treatment-resistant schizophrenia, the fact that the studies with positive results were unblinded and mostly nonrandomized could be interpreted in 2 ways. The positive findings are due to bias on the part of the treating clinicians, patients, and raters, or the patients in open studies are more representative of the severely ill patients who benefit most from clozapine but are less likely to enroll in complex and demanding RCTs.

Thus, the biggest concern about the validity of the findings from the meta-analysis by Samara et al[1] is the question regarding the generalizability of the samples that were enrolled into the blinded RCTs. Similar concerns have recently been raised about the evidence base of RCTs for long-acting injectable antipsychotics (LAIs) compared with oral antipsychotics in the maintenance treatment of schizophrenia. Here too, a disconnect was observed between the lack of a significant advantage of LAIs vs oral antipsychotics in RCTs as opposed to the superiority of LAIs in mirror-image and naturalistic study settings where patients at risk for nonadherence (those most suitable for LAI treatment) are likely more studied.[6] Thus, we agree with Samara and colleagues[1] that more research is needed to clarify the efficacy and effectiveness of clozapine. Because data suggest that, even in naturalistic, nationwide studies, clozapine's efficacy and effectiveness might diminish as it is used later in the illness,[7] we urge the field to conduct large, pragmatic RCTs that are designed to include patients who are as representative as possible of the target population to provide high-quality generalizable data that can address the current uncertainty around the role of clozapine in patients with treatment-resistant schizophrenia.

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