Clozapine, Long-Acting Injectables (and Polypharmacy?) Superior in U.S. and International Registries

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That replication is the essence of science may be even more the case for large, observational registry studies than for randomized controlled trials. Such registry studies are subject to multiple confounders, and particularities of the health systems analyzed may lead to different results. In this context, Weiser et al. (1), in this issue of the *Journal*, examined the Veterans Affairs database for time to discontinuation between available antipsychotics. They found that clozapine, long-acting injectables (LAIs), and polypharmacy outperformed other drugs and oral formulations. This finding is remarkably similar to those from Swedish and Finnish national databases in which Tiihonen et al. (2) and Taipale et al. (3) found that clozapine, LAIs, and some combinations of antipsychotics were the best treatments and that the combination of clozapine with aripiprazole was even better than clozapine alone in relation to rehospitalization (4). In a Hungarian national database, LAI risperidone (the only second-generation antipsychotic with an LAI formulation available at that time) was associated with longer time to discontinuation than a number of oral drugs, including clozapine (5). In a Dutch database, patients who had discontinued clozapine did best when they were rechallenged with clozapine (6). In contrast, Weiser et al. could not replicate the previous findings of superiority for clozapine, LAIs, and antipsychotic combinations in terms of rehospitalization.

The most likely reason for the superiority of LAI medications is improved adherence. Long-acting injectable medications are not intrinsically more efficacious than their oral counterparts, as has been shown by a meta-analysis of randomized controlled trials that included only those studies in which oral antipsychotics were compared with their LAI counterparts (7). Even when studies that compared different oral and LAI drugs were included in the most recent meta-analysis, the superiority of LAIs was minimal (number needed to treat of 50 or absolute risk difference of 2% [8]). Patients who consent to participate in randomized controlled trials are compliant per se, and this compliance is further supported by regular study visits and examinations. Therefore, the fact that in randomized controlled trials there are no clear differences between oral and LAIs strongly suggests that there is not an intrinsic difference in efficacy. In contrast, meta-analyses of "before and after studies" in which the time patients spent in the hospital in the year before they were put on LAIs is compared with the time spent in the hospital in the year after they were prescribed LAIs; LAIs are clearly superior (7).

The clozapine results could be a combination of better efficacy and improved adherence. Clozapine is considered to be the most efficacious drug, and therefore patients may stay on it longer. Additionally, clozapine use requires more regular contacts with the treatment team for blood count monitoring, which can improve adherence. In the Weiser et al. study, clozapine, LAIs, and drug combinations were not associated with less rehospitalization than other drugs, which also speaks against better efficacy. Similarly, previous findings that clozapine is associated with reduced mortality (9) may also have mainly to do with better monitoring and outcomes in clozapine-treated patients. On the other hand, clozapine use is associated with substantially lower risk of suicidal behavior than any other antipsychotic (10), and an alternative explanation for the failure to replicate clozapine's superiority in terms of rehospitalization is that the analytic approach was subject to residual confounders. Patients who receive clozapine and antipsychotic combinations are the most severely ill, and LAIs are also often given to patients with difficult-to-treat symptoms. The conventional between-individual analysis applied might not have sufficiently controlled for such an effect called "confounding by indication." In contrast, the more sophisticated within-subject approach used in the Swedish and Finnish analyses can better account for this problem, since patients are used as their own control.

That combinations of antipsychotics were associated with longer time to discontinuation but not for hospitalization in the present analysis could also mean that these drugs are used as a last resort.

The superiority of antipsychotic combinations in the present and previous registry analyses is the most controversial finding. In meta-analyses of blinded, short-term, randomized controlled efficacy trials, no superiority of combinations was detected in double-blind randomized controlled trials except for the addition of aripiprazole, which improved negative symptoms (11). However, those efficacy studies investigated severity of symptoms but not long-term effectiveness in relapse prevention. That combinations of antipsychotics were associated with longer time to discontinuation but not for hospitalization in the present analysis could also mean that these drugs are used as a last resort. Once a patient

receives a combination, the only evidence-based option is clozapine, and therefore patients may just stay on the combination. From the mechanism of drug action point of view, we do not entirely understand how the individual antipsychotics work except that they all bind to dopamine receptors. If two dopaminergic drugs are combined, the mechanism is even more obscure. For example, in the Tiihonen et al. study (4), the combination of clozapine and aripiprazole was associated with the lowest risk of rehospitalization, which has some plausibility because clozapine only binds to dopamine receptors by approximately 40%. Thus, adding a dopaminergic agent like aripiprazole may make sense, especially when these two drugs counterbalance each other's side effects and possibly lead to better adherence. Also, the lower dose of each antipsychotic during combination than during monotherapy treatment (3) may have a beneficial effect. These considerations are highly speculative, however. Unfortunately, Weiser et al. did not attempt to identify which combinations are superior.

Finally, while it is important to determine greatest efficacy when considering different treatments, it is equally important to discover the relative negative effects of treatment. One of the most important findings by Weiser et al. was that widely used quetiapine was associated with a 36% worse outcome in terms of hospitalizations compared with olanzapine, which is also well in line with previous results from the Finish and Swedish studies. The finding that first-generation oral antipsychotics are among the first antipsychotics in terms of time to discontinuation may not be surprising. Many patients who do not do well on old drugs might nowadays want to be quickly switched to second-generation antipsychotics. It should be kept in mind that first-generation and second-generation antipsychotics are heterogeneous groups of agents, and therefore this classification has been abandoned and replaced by the Neuroscience-based Nomenclature, which groups psychotropics according to their main mechanism of action (12).

The replication of findings from other countries in the Weiser et al. Veterans Affairs study makes a strong case for considering LAIs and clozapine in the United States. However, Kelly et al. (13) reported that according to the IMS Health Care Institute (14), the market share of clozapine in the United States has been steadily declining, accounting for 11% of all prescriptions for antipsychotics in 1999, 9% in 2000, about 4% in 2006, and 3% in 2008. Concerning antipsychotic combinations, sufficiently large and well-designed randomized controlled trials are needed to more fully understand why this is the case and to define which combinations of medications are the most effective.

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