Real-Life Dosing With Second-Generation Antipsychotics

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This is the first of 2 articles addressing methodological issues regarding real-life dosing and switching strategies when treating patients with second-generation antipsychotics.

When faced with nonresponse to an adequate duration of antipsychotic treatment at maximum recommended doses, clinicians have 4 basic options to improve symptomatic and/or functional response: (1) wait for the occurrence of a potentially delayed response; (2) augment with another medication (of the same or a different class); (3) switch to another medication (of the same or a different class); or (4) increase the dose beyond the upper dose range used in U.S. Food and Drug Administration (FDA) approval trials. If sufficient data were available, a fifth option could be to check for the presence of therapeutic antipsychotic drug levels. This fifth option will be addressed in the second part of this article.

Unfortunately, controlled data comparing the strategies mentioned above are scarce[1] but seem to indicate that, in chronically ill and refractory patients, waiting for a delayed response, increasing the dose, or switching to another antipsychotic may not be particularly helpful, with the exception of a switch to clozapine.[2,3]

The overall disappointing outcome of a switch from one antipsychotic to another nonclozapine antipsychotic in chronically ill patients with schizophrenia was reconfirmed by the recent publication of the first outcome data from the National Institute of Mental Health–sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial.[4] In this 18-month, randomized, double-blind study in patients with nonrefractory but chronic schizophrenia, switching patients to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone was associated with premature all-cause antipsychotic discontinuation in 64% to 82% of patients. Even more disconcerting was that the median time of "effective" treatment (defined as reaching a rating of "mildly ill" on the Clinical Global Impressions-Severity of Illness scale or of "moderately ill" if patients had been either severely or extremely ill at baseline) was only 3 months for olanzapine and 1 month for the remaining 4 antipsychotics.

While several potential confounding factors (e.g., proportion of patients randomly assigned to continue the previous treatment, exclusion of patients with tardive dyskinesia at baseline from the perphenazine treatment arm, lower total number of patients on ziprasidone treatment, inclusion of only 28% of patients with a recent exacerbation of symptoms in the past 3 months, and potential bias of investigators to more readily move patients to the second phase of the 3-phase study) complicate the interpretation of the observed outcomes in this study, the specific antipsychotic dose selection, a relevant issue in trial designs,[5] is of specific interest.

It is important to note that the only antipsychotic showing superiority in several outcomes (all-cause discontinuation, time to all-cause discontinuation, discontinuation for lack of efficacy and due to patient decision, duration of "effective" treatment, and hospitalization for illness exacerbation) was also the only one for which the maximum permitted dose exceeded the upper dose limit of 20 mg (by 50%) used in the FDA approval studies (i.e., 30 mg/day of olanzapine). Unless the reported differences in outcome are explained by the superiority of one drug compared with all other nonclozapine antipsychotics used in this trial, these results suggest that, in certain patient populations, antipsychotic doses above the recommended dose range may beneficially affect outcomes.

Limitations of Dosing Ranges Utilized in Registration Trials

The determination and interpretation of doses that were used in phase 4 clinical trials of antipsychotic medications is a complex issue.[6] As observed with almost all second-generation antipsychotics (the only clear exception being risperidone), the doses shown to be effective in registration trials appear to be somewhat lower than those required for a sizable number of patients in clinical practice.[7–9]

Although FDA-approved dose ranges are in place to limit marketing strategies and not necessarily clinical practice patterns, many physicians feel bound by the upper dose limits. Clinicians often opt to switch or augment rather than increase beyond this dosing range in patients who have only partially responded or are nonresponders despite a "maximum" dose for an appropriate duration, even if these patients do not exhibit rate-limiting side effects.

This "conservative" strategy, however, underestimates the differences in patients' pharmacokinetic and pharmacodynamic profiles, including drug metabolism, central nervous system drug penetration, and receptor characteristics; disease and symptom severity; and presence of comorbid disorders or comedications, among others.

Furthermore, certain elements of the clinical trial design that determined these dose ranges have to be considered when evaluating the validity and generalizability of these dose ranges. In designing these trials, the sponsor relies in part on preclinical data that may or may not predict clinical efficacy and safety observed in postmarketing experience.[10]

In addition, peripheral pharmacokinetics may not predict central pharmacodynamics, which is exemplified by the fact that most antipsychotics, even those having a peripheral half-life of less than 24 hours, can be given once daily without reduced efficacy. An example of this is quetiapine,[11] which has a peripheral half-life of approximately 7 hours.

Moreover, the pharmaceutical companies have to weigh the goal of showing superior efficacy against proving safety and tolerability. In placebo-controlled trials, the design is likely to err on the side of lower maximum doses. This way, efficacy will still be superior to placebo, but dropout rates and side effect frequencies remain favorable.

In addition to these methodological limitations, certain patient groups commonly encountered in clinical practice are systematically excluded from the very trials that define a supposedly effective dose range for a patient population at large: (1) treatment-refractory patients, (2) extremely ill patients, (3) patients with psychiatric comorbidities, and (4) patients in need of multiple psychotropic medications.

Treatment-refractory patients who arguably may require higher doses are generally excluded, as they would not generate a signal of efficacy for the novel compound. Extremely ill patients who are unable or unwilling to provide informed consent for a double-blind placebo-controlled trial are often too sick and lack sufficient insight to consent to a rigorously conducted study. Patients with recent substance abuse or dependence or other comorbidities are excluded in order to remove confounding factors that may hamper conclusive inter-

pretation of the study results. Finally, patients who are responders to the dose range used in these phase 4 trials respond to antipsychotic monotherapy, possibly with the early addition of a benzodiazepine. However, most patients with severe mental disorders are taking several medications, and the prescribing of an antipsychotic as the sole medication is often the exception rather than the rule.[12–14]

Research Agenda

In order to evaluate the question of real-life dosing ranges, postmarketing studies are necessary in a broad range of patients with generalizable illness and cotreatment features. Because of the increased number of potential confounds, these studies need to be large scale and, ideally, use a fixed-dose design.[15] Furthermore, because of interindividual patient differences in pharmacokinetic and pharmacodynamic variables, as well as uncertain medication adherence, antipsychotic dose may not be the most appropriate guiding criterion. These confounding factors may explain mixed results of the few high-dose reports with second-generation antipsychotics.[16]

Even though the potential use of serum antipsychotic level monitoring in optimizing response has been discussed, limited research has not provided conclusive data that could guide clinical practice, with the exception of therapeutic clozapine levels.[17,18] In view of the wide variability of plasma levels[19] and an incomplete association with symptom response,[20] novel study designs need to be considered.[21] These include the collection of plasma levels in large-scale trials to determine the range of plasma levels present in 95% of the responders.

Subsequently, nonresponders should be divided into those whose serum levels were below and those whose levels were within the "therapeutic" serum antipsychotic level range observed in responders. Patients with lower serum levels should be randomly assigned to supervised medication intake to rule out nonadherence or to dose increase until the therapeutic level of responders has been reached. The group with levels within the range observed in responders should be randomly assigned to placebo or to additional study medication to raise the serum level to a therapeutic range. Obviously, efficacy as well as safety and tolerability of high-dose strategies need to be assessed carefully, as an increased side effect burden is a major concern.

Conclusions

From a regulatory standpoint, the placebo-controlled design and limitation to patients with only the targeted disorder who receive monotherapy with the medication under investigation are crucial to detecting efficacy and safety signals that are unique to the new agent. However, clinicians need to remind themselves of the limitations inherent in the registration trials discussed above when hesitating to increase a dose of an atypical antipsychotic in a treatment-adherent patient with limited response and, particularly, insignificant side effects.

Although high-dose treatment with conventional antipsychotics has generally not been successful, this strategy was almost invariably associated with marked side effects. By contrast, the combined blockade of serotonin-2A and dopamine receptors, characteristic of second-generation antipsychotics, may allow for higher dosing strategies. Furthermore, before considering high-dose antipsychotic strategies, clinicians need to rule out the potential for nonadherence and the presence of either akathisia or parkinsonian side effects that may mimic enduring positive symptoms or negative or cognitive symptoms, respectively.

Controlled trials, ideally including the assessment of plasma antipsychotic levels, are needed to evaluate the efficacy of high-dose second-generation antipsychotic treatment strategies in patients with enduring and impairing symptoms.

In next month's ASCP Corner, I will discuss issues in the interpretation of studies that have evaluated different switching strategies for the initiation of second-generation antipsychotics, which is another common clinical scenario clinicians face when patients insufficiently respond to a given antipsychotic.

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