The Use of Depot Medications in the Treatment of Schizophrenia

An industry-sponsored randomized, double-blind trial of depot olanzapine for the prevention of relapse of schizophrenia is reported in this issue (1). Its publication raises several issues for readers who wish to use the results of the study to guide their clinical practice. First, what is the effect on the results of the study from the potential bias of the pharmaceutical company that sponsored it? Second, are depot medications safe and effective in chronic illness such as schizophrenia?

The most damaging industry bias is not publication of positive results, but the industry's repeated failure to publish negative results, which suppresses potentially informative data by placing these unwelcome results in the file drawer, where they are not readily accessible to most clinicians and other investigators. Second, the conclusions of industry-supported and -controlled trials as presented in their published abstracts favor the sponsor's drugs 90% of the time (2). Nonetheless, in the aggregate, enough trials have been published to provide a reasonably complete view of the effects of antipsychotic drugs in schizophrenia. Colleagues and I have independently reevaluated the results of these trials, blind to the identity of the sponsoring pharmaceutical company, and found that they do not show a statistically significant sponsorship bias (3). The publication of clinical trials, including those supported by industrial sponsors, enables each reader to assess the strategy and methodology of the study and then to examine the data in figures and tables to form an independent opinion of the soundness of the study, the robustness of the therapeutic effect, and the likelihood and seriousness of side effects. It is important that these papers be carefully refereed to be certain that each of these points is fully described and that the data are completely presented. A clinically important, well-conducted study, such as the one by Kane et al. in this issue, merits close reading by psychiatrists who treat patients with schizophrenia, as its data are a reality check on the more biased conclusions sometimes presented by industry-supported speakers.

"There are also very few rigorous clinical trials of maintenance therapy."

Efficacy in maintenance studies of schizophrenia is generally measured as the prevention of relapse. We would hope that a long-term treatment program that includes long-lasting medication might also modify the disease course, particularly because schizophrenia starts in adolescence and young adulthood and lasts throughout life. There are only a few depot medications available, however, and therefore depot olanzapine is a valuable addition to our pharmacopoeia. In addition, there are also very few rigorous clinical trials of maintenance therapy, and therefore those data in the study by Kane et al. merit additional examination, both for documentation of prevention of relapse and for evidence of longer-term improvement. Survival curves quantify the time to relapse under the active drug treatments, which in this study were various doses of depot olanzapine administered at 2- or 4-week intervals and an active comparator, oral olanzapine. The oral olanzapine group did surprisingly well, with 93% surviving without relapse for 24 months. Although this study is an efficacy study with patients preselected for compliance, the favorable results with oral olanzapine may be reassuring to readers who were dismayed by the short time that patients in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study continued to take their assigned drugs (4).

The study by Kane et al. was sufficiently powered to establish noninferiority, not mere failure to find significant differences. Their study suggests a dose-related effect for the

depot medication, with higher doses providing slightly more benefit in the standard range of 2- and 4-week doses: 150 mg every 2 weeks, 405 mg every 4 weeks, and 300 mg every 2 weeks. None of these regimens was inferior to the good response seen with the oral dose comparator. However, a low dose, 45 mg every 4 weeks, was significantly less effective, both in preventing relapse and in decreasing symptom scores. Scores on the Positive and Negative Syndrome Scale (PANSS) were 10 points higher in the low-dose group, indicative of a loss of control of the illness. Thus, there is some evidence for a longer-term benefit from continuous long-term treatment at adequate doses of medication, either oral olanzapine, for patients who can comply, or the depot preparation.

At steady state, the dose of 300 mg every 2 weeks produces blood levels similar to those achieved with the 20-mg daily oral dose. However, plasma levels decrease markedly after the first injection, and steady state is not reached until the third injection. Therefore, oral drugs should be continued at full dose for 2–4 weeks and then gradually decreased over a month or two. Rare (one per 200 injections) accidental intravenous administration can produce delirium or deep sedation, observed in 50% of subjects within 20 minutes and in the remainder within 3 hours. It may take as long as several days for the patient to recover, although all patients do recover. Patients should be observed for 3 hours after the injection to prevent accidents, such as falls or traffic accidents.

For depot medications, as for psychopharmaceuticals more generally, clinicians who ignore the patients' individual histories of response to drugs may doom their patients to receive drugs that they do not like, with resultant poor efficacy and intolerable side effects (4). When a depot formulation is contemplated, both the patient and the physician should have had experience with the oral formulation. Most efficacy difference between drugs occurs in the first month, and about 50% of the weight gain occurs in the first few months. Consequently, the experience with the oral formulation should guide drug choice for depot formulation, especially when a depot formulation has to be instituted because of the patient's nonadherence or frequent relapse, where there is evidence that change to a depot medication does decrease relapses (5).

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