Commentary on the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

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Since the introduction of the second-generation or so-called "atypical" antipsychotics in the mid 1990s, they have become far more widely used in the United States than the first-generation or conventional antipsychotics. Given the increased costs associated with these newer medications, attempts to delineate their potential advantages and disadvantages from a clinical, public health, and health economic standpoint are certainly important.

When evaluating the effects of antipsychotic drugs in schizophrenia, it is important to recognize the heterogeneity of the illness in terms of symptom patterns, severity, course, and treatment response (both therapeutic and adverse). Patients with schizophrenia present with positive, negative, cognitive, and other dimensions of symptomatology and functional impairment. These symptoms can worsen over time and can become less medication responsive. Patients' vulnerability to side effects or dosage requirements for optimum response can also vary over time.[1]

These and other factors contribute to the difficulties inherent in designing trials that can simultaneously address even a subset of the relevant questions in a truly generalizable fashion. In addition, many clinical trials of new medications are designed primarily for regulatory approval and labeling language and are generally sponsored by pharmaceutical companies. Most have both placebo controls and active comparators; however, the active comparator is usually given in 1 fixed dose or fixed dosage range, and the experimental drug might have more than 1 dose.

It is often suggested that the patients in these trials are not "real world" patients because they are recruited from research sites or academic hospital populations and must be willing to participate in double-blind and often placebo-controlled trials, among other reasons.

The CATIE study[2] was funded by the National Institute of Mental Health and was intended to compare the efficacy and tolerability of atypical and typical antipsychotics in the treatment of schizophrenia. The trial was intended to be "pragmatic," that is, a hybrid of efficacy and effectiveness trial designs. A total of 1460 patients who were judged to meet DSM-IV criteria and not be either in their first episode or "treatment resistant" were eligible for the trial. Concomitant medications, medical illnesses, and/or substance abuse disorders were allowed (in contrast to many trials conducted for regulatory purposes).

A key element (and source of misunderstanding) in the design of the trial was that patients were enrolled in a treatment program lasting up to 18 months, but which could include 3 different phases. This design differs from naturalistic or typical treatment in that patients and clinicians knew that there was a second and potentially third phase of the trial; therefore, discontinuing medication in the first phase could have been influenced to some extent by the availability (and the implicit or explicit desire to recruit subjects) of a second and third phase.

One source of confusion in discussing the outcome of the trial has been the understanding of the primary outcome measure: all-cause discontinuation. This outcome was not simply discontinuation of the initial treatment but also eligibility for the second phase of the study (which in my opinion was in many ways more interesting and potentially important than the first phase). In the second phase, participants who discontinued phase 1 could choose to be randomly assigned to clozapine (the only drug given open-label) or to olanzapine, quetiapine, or risperidone (given double-blind), or alternatively they could choose to be randomly assigned to ziprasidone or one of the other 3 atypicals (double-blind). Importantly, no one in phase 2 could be assigned to the same drug that they had been receiving previously. In contrast, when patients entered the first phase of the study, they could be randomly assigned to the drug that they had previously been taking, and this had an important impact on the results, as I shall discuss subsequently.

In phase 1, the study enrolled 1460 patients.[3] The mean age was 41 years, 74% were male, 60% were white, 35% were black, and 5% were other. In the previous 3 months, 28% had experienced an exacerbation of schizophrenia symptoms. Patients had first received antipsychotic medication a mean of 14 years previously. The mean Positive and Negative Syndrome Scale (PANSS) score at baseline was 76. Alcohol or drug dependence/abuse diagnoses were present in 25% and 20%, respectively (not mutually exclusive).

Although one of the goals of this study was to recruit a more representative sample than most industry trials, the age and chronicity of the patients is high—in fact, somewhat higher than in many industry trials. Mean time since first treatment was 24 years and since first treatment with antipsychotics was 14 years. This might not be the ideal population in which to study potential differences in medication effectiveness, as it is likely to be more representative of poor or partial responders. Although "treatment-resistant" patients were ineligible, *treatment resistance* was defined as "the persistence of severe symptoms despite adequate trials of one of the proposed treatments or prior treatment with clozapine." That definition leaves enormous room for interpretation, and it is likely that many poor responders were included.

Another area of controversy is dose equivalence. It is important to emphasize that establishing dose equivalence is a difficult task, and the optimum dose of haloperidol is still debatable, even after several decades of use. Optimum dose will differ from patient to patient and can differ across different phases of the illness, e.g., first-episode patients generally respond to lower doses than multiepisode patients.[4] Poor or partial responders might benefit from somewhat higher doses than robust responders,[5] and those in the maintenance phase might require lower doses than when they were acutely psychotic.[6] As Heres et al.[7] have suggested, dose ranges are crucial factors that potentially influence trial outcome and are problematic in comparisons between drugs.

The dosing and dose equivalence used in the CATIE study[2] were somewhat different than those suggested elsewhere. For example, the American Psychiatric Association Practice Guidelines for the Treatment of Patients with Schizophrenia[8] recommends 10 to 30 mg/day of olanzapine, 300 to 800 mg/day of quetiapine, 2 to 8 mg/day of risperidone, and 120 to 200 mg/day of ziprasidone. In CATIE, a maximum of 6 mg of risperidone and 160 mg of ziprasidone was used.

The dose equivalency used to yoke medications in CATIE also differed from that resulting from a survey of 50 experts in the treatment of schizophrenia.[9] Although the authors of the CATIE study state that "the average prescribed doses of these drugs in the United States for patients with schizophrenia during the period in which the study was conducted (14 mg of olanzapine per day, 3.8 mg of risperidone per day, 388 mg of quetiapine per day, and 125 mg of ziprasidone per day) were generally similar to the ones we

used,"[3 p1218] the mean modal doses in CATIE were, in fact, 43% higher for olanzapine, 40% higher for quetiapine, 11% lower for ziprasidone, and 3% higher for risperidone.

Although it is impossible to tell from the available data, if such differences in dosage and dosage equivalence do matter, this issue must be addressed, as it is an important concern for clinicians in deciding what doses are most appropriate and whether higher than usual doses should be tried before discontinuing a trial.

Interestingly, fewer than half of the patients participating in the first phase received the maximum dose allowed of their assigned medication[3]; yet, the rates of discontinuation due to intolerability ranged from 10% to 19%. Therefore, the question is whether the 15% to 28% of patients who discontinued due to lack of efficacy received the maximum allowable dose. Hopefully, future analyses and reports will address this and other issues related to optimum dosing in greater detail.

A major finding in the CATIE study[3] was an overall 74% discontinuation rate before 18 months, with approximately 50% discontinuing before 6 months. The time to all-cause discontinuation was significantly longer for olanzapine than quetiapine or risperidone but not in relation to perphenazine or ziprasidone (although fewer patients had been randomly assigned to ziprasidone, which was introduced while the study was already under way, thereby reducing the statistical power for this comparison). The time to discontinuation of treatment for lack of efficacy was significantly longer in the olanzapine group than in the perphenazine, risperidone, or quetiapine groups. There were no significant differences between the groups in time until discontinuation due to intolerable side effects.

One important element of the design was that patients with tardive dyskinesia (TD) at baseline (231 subjects) were not eligible to be randomly assigned to perphenazine. There were no significant differences between the medications in terms of the incidence of extrapyramidal side effects, akathisia, or movement disorders as reflected by rating scale data. The safety outcome measure revealed a higher incidence of apparent abnormal involuntary movements (13%–17%) than extrapyramidal symptoms (4%–8%) or akathisia (5%–9%). It appears that the baseline prevalence of TD was 16%; therefore, this rate did not change during the course of the study. It is also important to recognize that following a cohort of patients who have already been treated with antipsychotics for many years (mean 14 years since first exposure) when those with preexisting evidence of TD were not randomly assigned to the conventional drug is not necessarily an adequate test of potential differences in risk. Data from our long-term prospective study suggest that the risk of TD might diminish considerably after 15 years of treatment (J. M. K.; M. Woerner, Ph.D.; M. Borenstein, Ph.D.; et al., unpublished data, March 2006).

Olanzapine's apparent superiority in all-cause discontinuation was coupled with a significantly higher risk of weight gain, increased glycosylated hemoglobin, increased cholesterol level, and increased triglycerides level. Although significantly more patients taking olanzapine discontinued because of weight gain, it is likely that weight gain does not lead to as rapid a discontinuation of treatment as other adverse effects do, or as perhaps it should.

As was pointed out in a response to a letter to the *New England Journal of Medicine*,[10] approximately 15% of patients in CATIE were randomly assigned to the medication that they had been receiving prior to the study (in other words, they had no change in medication). Patients assigned to olanzapine or risperidone who had been receiving those medications prior to the study remained on their medication significantly longer than other patients. When these patients were removed from the intent-to-treat analysis, although the results of a sensitivity analysis were similar to the primary analysis, the overall test of the comparison of the treatments was not statistically significant regarding the primary outcome measure of all-cause discontinuation. It is also important to note that no difference was found between the 5 studied antipsychotics in the secondary efficacy measure of change in PANSS scores in this population with chronic schizophrenia.

Another interesting result is the proportion of time that patients were categorized as receiving "successful treatment." This category was defined as the number of months of treatment in which patients had a Clinical Global Impressions-Severity of Illness score of no more than 3 (mildly ill), or of no more than 4 (moderately ill) if they had improved at least 2 points from baseline. The mean time that enrolled subjects met these criteria was less than 2 months. The duration was significantly longer in the olanzapine group than the quetiapine, risperidone, or perphenazine groups and was significantly longer in the risperidone than the quetiapine group.

This statistic coupled with a 74% overall rate of discontinuation suggests that the medications we are currently using (and/or the methods with which we utilize them and other treatment modalities) leave much to be desired. Although there were some differences between medications, the potential advantages for olanzapine, for example, are mitigated by significantly greater adverse metabolic effects—even in a population that had in many cases already been treated with atypical antipsychotics (including olanzapine).

Although there can be considerable debate about the design and interpretation of any study, and no one study can adequately address the numerous questions relevant to the pharmacotherapy of schizophrenia, the CATIE results challenge us to develop better medications and better methods for improving outcomes. In the meantime, the data emphasize the importance of individualized treatment, clinical judgment, weighing benefits and risks, and shared decision-making.

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