*- Essential Psychopharma*Stahl*ogy -*

Will CATIE Change Your Practice?

A recent head-to-head study of antipsychotics may raise more questions than it answers

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What is CATIE?
CATIE, or the Clinical Antipsychotic Trial of Intervention Effectiveness, sponsored by the National Institute of Mental Health, is perhaps the largest, longest, most comprehensive and most expensive trial of antipsychotics in schizophrenia ever conducted without pharmaceutical sponsorship.

Specifically, about 1,500 "real world" patients with schizophrenia were prospectively randomized to one of four atypical or one conventional antipsychotic drug and then followed over 18 months. The trial originally included the atypical antipsychotics risperidone, olanzapine and quetiapine, and later ziprasidone was added, but aripiprazole was not included because it was not yet approved at the time when the study was being planned. The conventional antipsychotic that was included was perphenazine.

Why was this study conducted?
Even with millions of patients taking billions of dollars worth of antipsychotics in the United States each year, it is not yet clear whether any one drug is better than another. Head-to-head comparisons of antipsychotics have been mostly sponsored by manufacturers who conduct them for registration and marketing purposes. The results have consistently shown efficacy better than placebo, which may be useful to the FDA for approving a drug for marketing, but not that useful to a clinician trying to decide which antipsychotic to prescribe for a specific patient, or to a formulary committee trying to decide which antipsychotics to include and which to restrict from payment.

Those head-to-head studies that have been conducted by pharmaceutical sponsors tend to include comparisons of only two or three drugs, to exclude "real life" patients with other problems such as substance abuse, and to be designed to yield outcomes that favor the sponsor's drug. Thus, CATIE was designed to fulfill the need for a large study of all available treatments in real world patients conducted by an independent sponsor.

What are the findings?
The study's primary outcome was how long it took for patients to drop out of the study for any cause. The bad news is that overall, three out of four patients discontinued whatever drug they were on before 18 months of treatment. The good news is that there were some interesting differences among the six agents with three receiving blue ribbons in three different categories.

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Ziprasidone gets the blue ribbon for safety
Prior to the CATIE trial, if anything, there were safety concerns as well as efficacy concerns about ziprasidone. Imagine the surprise when ziprasidone not only showed no significant QTc prolongation, but was the only drug that actually improved the metabolic variables (triglycerides, total cholesterol, glycosylated hemoglobin) as well as weight. Furthermore, efficacy was comparable to the other agents despite its likely underdosing at 113 mg/day.

Now we can ask whether ziprasidone should be used preferentially in patients with metabolic problems such as diabetes, obesity, or the metabolic syndrome. We could even ask whether ziprasidone should be used preferentially in patients before they develop metabolic problems, such as in those with only a family history of diabetes or acutely elevated triglycerides, an indication of insulin resistance, while taking a different atypical antipsychotic.

Olanazapine gets the blue ribbon for effectiveness
The primary outcome measured in CATIE was time to dropout from any cause, a measure that tries to balance both efficacy and safety as a measure of "effectiveness." Olanzapine patients stayed in the trial significantly longer compared to the other drugs. There was a trend for olanzapine to show more efficacy but also more metabolic side effects, yet the balance of these factors as measured by time to dropout from any cause was that patients stayed on olanzapine longer than they did on the other drugs. Whether this is due to more effectiveness of olanzapine or to a more effective dose (20 mg olanzapine was compared to 3.9 mg of risperidone, 543 mg of quetiapine, 113 mg of ziprasidone, and 21 mg of perphenazine) can be debated. Although it is possible that higher doses of the other drugs would have led to their greater effectiveness, this cannot be assumed and will require further studies in order to determine.

Although there have been growing concerns about the metabolic side effects of olanzapine, there have not been similar concerns about its efficacy and the CATIE findings for olanzapine suggest that it might indeed have some efficacy advantages over other antipsychotics. Now the question can be posed whether these findings are robust enough and the risk/benefit ratio favorable enough to propose that olanzapine be tried in anyone without metabolic risk factors who has not had a full remission on a previous medication trial?

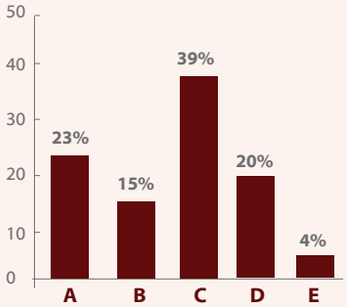
Perphenazine gets the blue ribbon for lowest cost with reasonable safety and efficacy
Another surprise from CATIE is how well patients did on perphenazine. Many head-to-head registration studies of atypical antipsychotics with conventional antipsychotics have shown comparable overall efficacy but better tolerability especially for motor side effects. Recent

Figure 1

In a recent poll of 217 mental health professionals, nearly 40 percent of respondents reported that the CATIE study did not significantly affect their prescribing practices.[2]

The results of the CATIE study have influenced my antipsychotic prescribing practices.

A. Strongly disagree
B. Disagree
C. Neither disagree or agree
D. Agree
E. Strongly agree



studies suggest that atypicals may have better efficacy than conventional antipsychotics do for cognitive symptoms. Thus, it was widely assumed that the dropouts from all causes would be high for perphenazine, but in fact they were comparable to the other drugs.

The real winner from CATIE may be the clinician.

The patients in this trial were not acutely ill and were not given perphenazine if they had tardive dyskinesia. The results suggest that it would be premature to write conventional antipsychotic drugs off entirely. There may be a subset of patients for whom moderate doses of conventional antipsychotics will be relatively well tolerated and for whom antipsychotic efficacy will be relatively well accepted. If so, this would be less costly. Payers are now asking whether the standard of care should be revised to allow more use of conventional antipsychotic drugs.

The bottom line—The real winner from CATIE may be the clinician (see Figure 1), who has always recognized that for most patients, there is no one antipsychotic that is clearly more effective or better tolerated than all the others for most cases. The huge variation of individual responses to specific drugs trumps a "one size fits all" or "start all patients on this drug first" approach. However, it will be interesting to see if there is now a rationale for sequencing the antipsychotics depending upon patient profile according to some of the lessons learned from CATIE.

TAKE-HOME POINTS

1. Several questions were raised but not settled by the CATIE study, including how effective or safe is any antipsychotic? Three out of four patients dropped out no matter what antipsychotic they took. However, the overarching question may be: is there now a rationale for sequencing the antipsychotics depending upon patient profile?

2. Is one antipsychotic safer or better tolerated than another? Looks like ziprasidone has the best metabolic and tolerability profile but aripiprazole was not included in this study. Now the question is: should ziprasidone be used preferentially in patients with diabetes, obesity, hyperlipidemia, and/or the metabolic syndrome?

3. Is one antipsychotic more effective than another? Patients on olanzapine took several weeks longer to drop out of the study, but also took a relatively higher dose. The question may now be: should olanzapine be tried in anyone without metabolic risk factors who has not had a full remission on a previous medication trial?

4. Is one antipsychotic more cost effective than another? The conventional antipsychotic perphenazine performed surprisingly well both in terms of safety and in terms of efficacy. The question being posed now by some: is reducing the risk of motor side effects and tardive dyskinesia worth the cost of new medication when effectiveness of conventional antipsychotics may be comparable to the newer agents, particularly for patients who respond well and tolerate low to moderate doses?

5. The conclusion for the immediate future: choosing a specific antipsychotic for a given patient remains an art and not a science.

References

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Publication Information

PsychEd Up—ISSN:1553-8907 (print), 1553-8915 (online)—is published monthly by NEI Press.