The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) is the largest study involving comparative effectiveness of antipsychotic agents ever completed in schizophrenia. Phase I of the study compared treatment of 1460 patients with schizophrenia using five antipsychotic medications: olanzapine, risperidone, quetiapine, ziprasidone, and the first-generation agent perphenazine. The study was initiated by the National Institute of Mental Health in January 2001, and the primary results of phase I were published in September 2003 in The New England Journal of Medicine. Baseline data on the prevalence of metabolic abnormalities in this population as well as an estimate of increased risk for cardiovascular disease in these patients have also been published separately. These initial data informed the clinical use of antipsychotic agents in the treatment of schizophrenia and constitute the largest study involving comparisons of antipsychotic medications, as indexed primarily by time to discontinuation for any cause and also by key secondary measures. Patients were initially assigned to treatment with perphenazine, olanzapine, quetiapine, or risperidone and followed for up to 18 months. Ziprasidone was introduced to the CATIE trial in January 2002 after approximately 40% of the sample had been enrolled. Comparisons involving the ziprasidone group were limited to the cohort of patients randomized after the addition of ziprasidone (n = 889). See Figure 1 for the overall design of the trial.

Eligible patients were 18 to 65 years of age and had a diagnosis of schizophrenia. Patients with comorbid conditions such as substance abuse or mood disorders were included. The primary outcome measure of CATIE, all-cause treatment discontinuation, was selected as a metric that integrates efficacy, safety, and tolerability outcomes. Secondary outcome measures are listed in Table 1. The study design was therefore intended as a practical clinical trial that sought to determine real-world effectiveness of these medications including phase I data regarding treatment effects on cognition and cost-effectiveness, phase II results, and further evaluations of the metabolic effects of these medications.

**TABLE 1. Secondary Outcome Measures**

- Psychopathology
- Neurocognitive assessment
- Safety
- Service utilization and costs
- Neurologic side effects
- Adherence to treatment regimen
- Quality of life
- Substance abuse
- Violence/aggressive behavior

Sources: Lieberman JA et al.1 Stroup TS et al.2 and JP McEvoy, MD, personal communication.

**Figure 1. CATIE Schizophrenia Trial Design**

Phases of the CATIE schizophrenia trial: Phase I compared five antipsychotic medications—olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. The primary outcome measure was discontinuation due to any cause. Secondary outcome measures included discontinuation due to adverse events or due to side effects. The study aimed to determine real-world effectiveness of these medications including phase I data regarding treatment effects on cognition and cost-effectiveness, phase II results, and further evaluations of the metabolic effects of these medications.

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Overview of Results
Of the 1432 patients who received at least one dose of the assigned study medication, 1061 (74%) discontinued the medication before 18 months for any cause. Although this rate may seem fairly high, it is important to note that a substantial proportion of the patients who discontinued treatment in phase I continued treatment in phase II, where they were switched to another medication. In fact, more than 50% of patients completed the full 18 months of the study, albeit in most cases on a different medication than initially assigned. These results reflect the common occurrence of medication switching in patients with schizophrenia, while also demonstrating the potential for ongoing treatment adherence for most patients.

The percentages of patients who discontinued for any cause were as follows: olanzapine, 64%; perphenazine, 75%; quetiapine, 82%; risperidone, 74%; and ziprasidone, 79%. The time to discontinuation of medication for any cause was longest (ie, most favorable) in the olanzapine group, and the differences were statistically significant for discontinuation due to intolerable effects (18%), with half of these discontinuations due to weight gain or metabolic effects. The highest rate of discontinuation due to extrapyramidal effects was seen in the perphenazine group (8% vs 2% for ziprasidone group). There were no significant differences in time to discontinuation due to intolerable side effects revealed no statistical differences in time to discontinuation, including lack of efficacy and intolerability. The time to discontinuation due to lack of efficacy was significantly longer in the olanzapine group than that in the quetiapine, risperidone, or perphenazine groups (all P < 0.001). There was no statistical difference compared with ziprasidone after adjustment for multiple comparisons. There were no significant differences among the risperidone, quetiapine, ziprasidone, or perphenazine groups.

Comparisons between agents for discontinuation due to intolerable side effects revealed no statistical differences in time to discontinuation, but significant differences in the rates of discontinuation. Olanzapine had the highest rate of discontinuation due to intolerable effects (18%), with half of these discontinuations due to weight gain or metabolic effects. The highest rate of discontinuation due to extrapyramidal effects was seen in the perphenazine group (8% vs 2% for the other groups).

Although CATIE was not rigorously designed to evaluate cardiovascular effects on the QT interval, there were no substantially different effects of the medications on the corrected QT interval seen on electrocardiography. Olanzapine showed significantly greater time to all-cause discontinuation than quetiapine or risperidone. There were no statistical differences among the risperidone, quetiapine, perphenazine, or ziprasidone groups in time to all-cause discontinuation. Olanzapine demonstrated the highest rates of discontinuation due to intolerable side effects.

Dosing
When assessing the clinical applicability of the CATIE findings, one must take study dosing into consideration. Although dose ranges of all the agents were suggested by the study investigators in consultation with the manufacturers, clinical practice regarding optimal doses of these medications have, in some instances, changed since the study was initiated. Figure 2 shows the differences between mean dose for each drug in the CATIE study and the mean dose currently used in clinical practice. For most agents, mean doses were higher than those currently used in clinical practice, particularly for olanzapine for which the mean modal dose in CATIE was 20.1 mg/day compared with an average of 15.9 mg/day in current clinical practice. The risperidone dose was similar to that used in clinical practice (3.9 mg/day in CATIE vs 3.5 mg/day in current practice). Ziprasidone was the only study agent that was used at a lower dose than is currently standard in clinical practice (11.5 mg/day in CATIE vs 13.7 mg/day in current practice) (Verispan (Yardley, Pa.) unpublished data, October 2005).

The panel consensus was that ziprasidone and olanzapine in particular appear to have been dosage outliers from clinical practice, with ziprasidone dosed relatively lower and olanzapine dosed relatively higher than other agents. Also noted was the lack of an explicit requirement to dose study medication with food, which might have affected the ziprasidone group, since food increases...
ziprasidone’s absorption substantially (up to twofold).

- Dosing in CATIE was somewhat different from current clinical practice dosing
- Mean modal doses in CATIE were higher for olanzapine and quetiapine and lower for ziprasidone than mean doses used in current practice

## Metabolics

The baseline data from CATIE revealed that rates of metabolic disturbances are even higher than previously thought in this patient population. The panel agreed that this important finding of CATIE has significant public health implications and should impact treatment approaches for patients with schizophrenia.

In an analysis of the CATIE baseline data, McEvoy and colleagues assessed the prevalence of the metabolic syndrome in 1,460 patients in the study. The criteria used to define the metabolic syndrome are shown in Table 2. These criteria were derived from the American Heart Association (AHA) definition, which uses a fasting glucose threshold of ≥100 mg/dL to define the metabolic syndrome. Alarmingly high rates of metabolic abnormalities were observed in the CATIE population at baseline. Seventy-three percent of all women and 37% of all men met the criterion for increased waist circumference (a measure of visceral adiposity). Fifty percent of men and 44% of women met the criteria for hypertension. In the subset of confirmed fasting subjects (n = 689), 49% of men and 63% of women had clinically significant baseline high-density lipoprotein cholesterol abnormalities, and 51% of men and 42% of women had fasting triglyceride levels above the metabolic syndrome threshold. Twenty-six percent of fasting subjects had impaired fasting glucose at baseline (≥100 mg/dL), placing them at high risk for the development of type 2 diabetes mellitus. The overall prevalence of the metabolic syndrome among the fasting cohort of CATIE subjects was 43% (based on AHA criteria) [see Figure 3] compared with 24% in a matched control population. (Comparative analyses used an age-, gender-, and ethnicity-matched control sample of subjects randomly selected from the third National Health and Nutrition Examination Survey [NHANES III] database.)

### Table 2. Diagnostic Criteria for the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td>Man: &gt; 40 in (&gt;102 cm)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Men: &lt;40 mg/dL, 50 mg/dL Women: 50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/885 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol.  
*≥3 risk factors constitute the metabolic syndrome.  
Source: Adapted from McEvoy JP et al.  
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### FIGURE 3. Prevalence of Metabolic Syndrome at Baseline in Fasting CATIE Trial Subjects

- 43% of CATIE subjects had metabolic syndrome at baseline  
- Less than 5% of CATIE subjects were treated with glucose-lowering drugs and less than 5% of CATIE subjects received cholesterol-lowering drugs  
- Male CATIE subjects had a 34% greater risk of developing CHD than female CATIE subjects had a 50% greater risk of CHD than is seen in the general population

### Clinical Implications of CATIE Phase I

The CATIE trial has provided a wealth of new data regarding the similarities and differences between medications used to treat schizophrenia. Although olanzapine offered some advantages in time to discontinuation, this came at the cost of the highest rate of deleterious effects on weight, lipid levels, and glucose levels. Olanzapine worsened all metabolic parameters, the use of agents like ziprasidone, which carry a favorable metabolic profile, could be considered for patients before significant metabolic complications arise.

Risperidone showed effectiveness similar to that seen with risperidone, quetiapine, and perphenazine but was the only agent in the study shown to be associated with improvement in weight, lipids, and measures of glycemic control. Participants noted that given the data showing a high prevalence of metabolic abnormalities in this population, the reduced likelihood for patients to receive adequate medical treatment, and the evidence for differential effects on weight and metabolic parameters, the use of agents like ziprasidone, which carry a favorable metabolic profile, could be considered for patients before significant metabolic complications arise.

Olanzapine showed effectiveness comparable to that of quetiapine, ziprasidone, and perphenazine and showed the lowest rate of discontinuation due to intolerable side effects (10%). Quetiapine was, however, the only agent associated with a substantial increase in prolactin levels.

Quetiapine showed effectiveness comparable to that of the other agents except olanzapine. Similar to olanzapine, quetiapine was associated with worsening of all metabolic measures, including weight, glucose, cholesterol, and
Observations on CATIE

triglycerides, although these changes were less severe than those seen with olanzapine. Quetiapine was associated with a significantly higher rate of anticholinergic effects than those observed with the other agents (P<0.001). Perphenazine in this study showed efficacy similar to that of all other agents except olanzapine and was generally well tolerated. Perphenazine was not associated with significantly higher rates of movement disorders than those seen with the other agents, although it did have the highest rate of discontinuation due to extrapyramidal side effects. As the panel noted, the study was not designed to fully examine the relative risk of developing movement disorders, particular tardive dyskinesia (TD), with perphenazine as compared with the risk of the other agents. Patients with TD were not assigned to perphenazine, and the average time on medication was too short to fully assess the risk of developing TD. The role of perphenazine in the modern treatment of schizophrenia remains unclear.

Olanzapine
- Longest time to all-cause treatment discontinuation
- Greatest deleterious effects on metabolic parameters

Ziprasidone
- Effectiveness similar to that of risperidone, quetiapine, and perphenazine
- Only agent associated with improvement in weight, lipids, and measures of glycemic control

Risperidone
- Effectiveness similar to that of ziprasidone, quetiapine, and perphenazine
- Lowest rate of discontinuation due to intolerable side effects
- Only agent associated with a significant increase in prolactin levels

Quetiapine
- Effectiveness similar to that of ziprasidone, risperidone, and perphenazine
- Associated with worsening of all metabolic measures
- Associated with the highest rates of anticholinergic effects

Perphenazine
- Efficacy similar to that of risperidone, quetiapine, or ziprasidone
- Highest rate of discontinuation due to movement disorders

The CATIE trial has challenged clinicians to raise the standard of care for patients with schizophrenia. Effectiveness is a composite measure of efficacy, safety, and tolerability. Most clinicians already incorporate this concept in their practices by discussing with patients the relative risks and benefits of the available medications and then matching treatment to individual patient characteristics. With the new data available from CATIE, it is clear that a patient’s overall health status—including weight, lipid profiles, and other metabolic parameters—should be a factor in the decision-making process.

Beyond Phase I
If the initial treatment in phase I was discontinued, the patient moved to the next phase of the study to receive a new treatment. Phase II was designed to have two separate study groups, one for patients who discontinued phase I because of lack of efficacy and the other for patients who discontinued phase I because of lack of tolerability. Patients who discontinued because of lack of efficacy were randomized to receive either clonazepam or a second-generation antipsychotic (olanzapine, quetiapine, or risperidone), testing whether clonazepam offered a treatment advantage to those patients. Patients who discontinued their first medication because of tolerability issues were randomly assigned to receive either ziprasidone or another second-generation antipsychotic (olanzapine, quetiapine, or risperidone), testing whether ziprasidone offered a treatment advantage to those patients.

Patients who discontinued their medication during phase II entered phase III for open-label treatment with a variety of medications, either alone or in combination.

Implications of CATIE Beyond Schizophrenia
It is appropriate for clinicians to be aware of and consider the CATIE data when treating patients in other psychiatric diagnostic categories where there is also evidence for an increased prevalence of metabolic risks. Although a similar assessment of comparative antipsychotic effects in bipolar disorder is not currently available, results from the large Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study will provide insights into the effectiveness of treatments for bipolar disorder.

Conclusion
The article on CATIE phase I data published in September 2005 in The New England Journal of Medicine is an initial report, and all of the data from this study have not yet been released. Publication of data regarding additional key outcomes is anticipated within the next year. These will include effects on cognition and cost-effectiveness data from phase I as well as phase II and phase III results, and dosing issues. Until these results are available, final conclusions regarding comparative outcomes cannot be made.

The results of CATIE undoubtedly will have far-reaching effects that likely will help shape both clinical practice and future studies. CATIE provides the opportunity—and a mandate—for clinicians to reevaluate how they choose pharmacologic treatment regimens for individual patients based on objective evidence. The high rate of metabolic disturbances and low rate of treatment observed in this patient population raise the importance of considering the overall health status of patients with schizophrenia. The data from CATIE support the importance of patients having access to all available therapies to ensure optimal treatment efficacy.

CATIE provides evidence to match medication profiles to individual patients’ needs
Access to all available medications is key to ensuring optimal outcomes

References