

## **The CATIE Study: Frequently Asked Questions**

- What is the CATIE study?
- How was CATIE conducted?
- Does the CATIE study prove that older antipsychotics are interchangeable with atypical antipsychotics?
- What questions did CATIE Phase 1 leave unanswered?

### **What is the “CATIE Study?”**

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study, funded by the National Institute of Mental Health (NIMH), is a nationwide three-phase clinical trial comparing the effectiveness of older and newer antipsychotic medications used to treat schizophrenia. CATIE is the largest, longest, and most comprehensive independent trial ever conducted to study pharmacotherapies for schizophrenia.

#### **Purpose of the Study.**

The purpose of the CATIE study, which was conducted between January 2001 and December 2004, was to examine the effectiveness of antipsychotic medications in a large and diverse population of consumers with schizophrenia, over a relatively long period of time, in a variety of treatment settings. Through CATIE, NIMH sought to research the effectiveness of treatments for schizophrenia under “real world” conditions, as opposed to the tightly controlled conditions—and limited populations—that are usually included in clinical trials for medications. In addition, CATIE compared antipsychotic treatments to each other, rather than to a placebo, as is usually done in clinical trials.

#### **Release of Study Results.**

The study results are being released in three phases.

Phase 1 – Results were released in the September 22nd issue of the *New England Journal of Medicine*. The findings compared all-cause discontinuation rates, efficacy and side effects across the five study drugs, which included one older generation antipsychotic and four second generation (also called atypical) antipsychotic medications.

Phase 2 – Results were released on April 1, 2006 in the *American Journal of Psychiatry*. Phase 2 compared atypical antipsychotics with each other in two different groups of participants. One group was randomized to treatment with clozapine if they failed one of the initial study medications. The other group took part in a medication trial which used ziprasidone and not clozapine.

Phase 3 – Results will include descriptive data on patients treated with aripiprazole (Abilify), which was added to the study after its approval in 2004. The date for the release of these results is unknown.

According to CATIE researchers, subsequent releases of data will also examine results in the following areas: cost-effectiveness (both for medication and across all health expenditures); cognitive improvement; rates of recovery; patient value of treatments in terms of functional performance; and reversibility of side effects. According to NIMH, “As additional results from CATIE are analyzed, disseminated, and put into context, the hope is that the cumulative findings will yield a more complete picture of the interaction between patient characteristics, medication, environment, and outcomes.”<sup>[1]</sup>

“*Cumulative findings*” is the key term here. Once all of the CATIE findings have been released, they could provide an extremely valuable tool to help consumers with schizophrenia and their clinicians make more informed choices about which treatment is best for each individual. However, as it currently stands, **CATIE**

**findings are still far from complete, and in most cases are inadequate to guide individual treatment decisions or inform public policy.**

## **How was CATIE conducted?**

### **Study Participants and Sites.**

The CATIE clinical trials included 1,460 [\[2\]](#) participants at 57 clinical sites across the country.

- Participants in the study ranged in age from 18 to 65 years old, and all had a diagnosis of schizophrenia (individuals experiencing first-time episodes and treatment-refractory schizophrenia were excluded from the study). Seventy-four percent of the participants were male.
- Many participants had co-occurring health and mental health problems, such as depression (28% of participants), anxiety (at least 14%), drug dependence/abuse (29%), diabetes (11%) and hypertension (20%).
- Sixty percent of participants identified themselves as white/Caucasian; 35% as African American/Black; 12% as Spanish, Hispanic or Latino; 2% as Asian; less than 1% as American Indian or Alaska Native; less than 1% as Native Hawaiian or other Pacific Islander; and 2% as “two or more races.” [\[3\]](#)
- According to researchers at an NIMH briefing on September 26, 2005, about 30% of CATIE participants were recruited during a hospitalization that resulted from an individual’s previous decision to discontinue medication. Data was not provided, however, on the reasons for these decisions.
- CATIE was conducted at many different treatment sites—including private clinics, academic centers, Veterans Administration hospitals, and public mental health centers—in an attempt to be broadly representative of the real-life settings where

consumers receive care.

- In typical clinical trials for FDA approval of antipsychotics, participants are followed for four to eight weeks. Participants in CATIE were followed for 18 months so that investigators could evaluate longer-term consumer outcomes.

### **Study Phases.**

The CATIE trial includes three phases. In Phase 1, participants were randomly assigned to one of four newer, "atypical" antipsychotic medications: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and ziprasidone (Geodon); or to one older-generation antipsychotic, perphenazine (Trilafon). No participants received placebos. Participants continued to take this medication for the next 18 months, or until one of the following occurred:

- the medication could not control their symptoms adequately;
- they developed an intolerable side effect; or
- they decided to stop the medication, or withdraw from the study for some other reason.

In Phase 2, Of the 1,052 participants with DSM-IV diagnosis of schizophrenia who discontinued phase 1 treatment before 18 months, 509 left the study entirely, 99 participants entered the efficacy pathway, and 444 entered the tolerability pathway.

- The efficacy pathway compared clozapine to the other newer atypical antipsychotic medications. Participants who chose this pathway either agreed to be assigned to clozapine, which they received open label (with knowledge of what they were receiving) or were randomly assigned to receive one of the other study medications (olanzapine, risperidone, or quetiapine) different from the one they took in phase 1.

- The tolerability pathway compared ziprasidone to the other study medications. Participants who chose this pathway were randomly assigned to receive either ziprasidone or an atypical medication different from their phase 1 medication.

### **Outcomes Measured.**

During Phase 1, the primary outcome measure studied was the rate of treatment discontinuation, for any reason (e.g., lack of efficacy, troublesome side effects, or other reasons). Secondary outcome measures studied included measures for clinical and functional outcomes, safety and neurocognition. These are the findings that were reported in the *New England Journal of Medicine* on September 22, 2005.

During Phase 2, in the efficacy pathway, the primary outcome measure was the time until discontinuation for any reason. Secondary outcomes include time to discontinuation for inadequate therapeutic benefit, intolerable side effects, or patient decision. In the tolerability pathway, the primary outcome measure was the same as the efficacy pathway. A key secondary outcome was the reason for treatment discontinuation as judged by the study doctor and secondary safety and tolerability outcomes. Results from phase 2 of the study analyzed effectiveness, efficacy and tolerability of many of the atypical antipsychotics available as well as an older medication, clozapine. These findings were reported in two articles in the April 1, 2006 issue of the *American Journal of Psychiatry*.

During Phases 2 and 3 of CATIE, participants whose assigned treatment was discontinued during Phase 1 could receive other treatments, and investigators followed their progress.

In addition, the investigators will continue to study other outcomes, including cost-effectiveness, quality of life, and

predictors of response to given medications. The Phase 3 findings have not yet been released.

### **Findings to Date.**

The CATIE Phase 1 trials found that in each of the five medication treatment groups, a majority of participants discontinued their assigned treatment due to inefficacy, intolerable side effects, and/or other reasons. Olanzapine (Zyprexa) had the lowest rates of discontinuation, but was also associated with higher rates of side effect such as greater weight gain and increases in measures of glucose and lipid metabolism. Specifically, 64% of those assigned to olanzapine discontinued the treatment before 18 months, followed by risperidone (74%), perphenazine (75%), ziprasidone (79%) and quetiapine (82%).

In short, each of the medications worked well for some individuals, but not others. The high treatment discontinuation rates are disappointing, but echo what many consumers and families have experienced—that it often requires trying more than one medication before finding the treatment that is effective for each individual. CATIE findings are consistent with previous research and clinical experience that has shown that complex factors—such as ethnicity, co-occurring illnesses and tolerance of side effects—all impact an individual’s response to a medication.

Across the treatment groups, an average of 39% discontinued their treatment due to inefficacy or intolerability, 30% due to decisions by study participants and/or their advocates, and 5% for other reasons. We do not yet know why some people responded well to each medication while others did not, or the reasons why some participants (or their patient advocates) chose to discontinue the medications.

In CATIE Phase 2, the main results of the efficacy (clozapine)

pathway indicated that clozapine was remarkably effective in this group of study participants and was substantially better than all the other atypical medications: 20 out of 45 patients (44%) who received clozapine were able to stay on clozapine for the rest of the study, whereas only eight out of 45 patients (18%) who received another atypical antipsychotic medication were able to stay on that medication to complete the study. The participants taking clozapine remained on it for an average of 10 months compared to an average of three months for those taking any of the three other medications. Those taking clozapine also had greater symptom reduction than those who took any of the other medications. Only one patient developed one of the most severe adverse side-effects, agranulocytosis (and was taken off clozapine).

The main results of the tolerability (ziprasidone) pathway indicated that about 35% of the participants who took olanzapine or risperidone were able to continue on their medication until the end of the 18 months of the study. This compares to only 23% of those who took ziprasidone and 16% of those who took quetiapine that were able to continue.

It was important to examine the results in phase 2 separately for those participants who had stopped their phase 1 medication for different reasons. For those who had stopped phase 1 medication due to inadequate management of psychotic symptoms, those taking olanzapine or risperidone in phase 2 stayed on their medication for a significantly longer duration than those taking quetiapine or ziprasidone, results that are similar to the overall results above. However, for the participants who had stopped phase 1 medication due to side effects, there were no significant differences among the four phase 2 medications. Thus, which medication works best depends in large part on why a patient was switched to it. □ Both phase 1 and 2 of the study confirm that a complete range of medications is necessary to help consumers and their caregivers find the treatment that works best for them.

## **Does the CATIE study prove that older antipsychotics are interchangeable with atypical antipsychotics?**

Absolutely not. Unfortunately, this misinterpretation was widely disseminated through the media when the Phase 1 results were published in 2005. In fact, the study strongly reinforces what consumers and families have known for years—that there is no “one size fits all” treatment for schizophrenia. Moreover, the study demonstrates that significant further research is needed into better treatment options for individuals and the impact that factors that are not measured in randomized controlled-trials have in successful clinical and functional outcomes.

- In the CATIE trials, no one drug was found to be effective for the majority of consumers. This reinforces the position that “fail-first” policies are clinically unsound.

- While study participants across the medications experienced a range of side effects, there were differences between drugs in the types of side effects that caused treatment discontinuation. For example, perphenazine (the older antipsychotic) was associated with more discontinuation for extrapyramidal side effects than the other drugs, whereas olanzapine was associated with more discontinuation for weight gain or metabolic effects. In Phase 2, in the efficacy pathway, insomnia was most common side effect with risperidone, anticholinergic<sup>[4]</sup> symptoms were associated with quetiapine and sialorrhea<sup>[5]</sup> was most common with clozapine. In the clozapine group, one patient had a serious adverse event of eosinophilia<sup>[6]</sup> and one patient developed agranulocytosis<sup>[7]</sup>, these patients discontinued use of clozapine. In the tolerability pathway, patients receiving risperidone experienced higher rates of adverse effects involving sexual functioning and galactorrhea<sup>[8]</sup>. Patients on olanzapine experienced more weight gain.

- Only one older antipsychotic medication—perphenazine—was

included in the CATIE trial. According to NIMH, one commonly-prescribed older antipsychotic, haloperidol (Haldol), was not included in the study because:

- “patients who take haloperidol experience high rates of movement side effects, called extrapyramidal side effects (EPS), such as rigidity and stiff movements, persistent muscle spasms, tremors, and uncontrollable restlessness. Because many individuals find EPS particularly difficult to tolerate, haloperidol is an unpopular treatment choice for many people with schizophrenia. Although EPS is associated to some degree with all the older ‘typical’ antipsychotic medications, perphenazine is an effective older antipsychotic that is less likely to produce EPS.” [\[9\]](#)
- Yet, in common clinical practice, Haldol is the more-frequently used older antipsychotic medication. Moreover, many Medicaid preferred drug list debates have focused on Haldol as a first-line or preferred treatment over the atypical medications.
- Among the study participants who took perphenazine, only 25% found it effective and tolerable enough to continue treatment. Given that the success rate was no better than that of the other study drugs, it would clearly be inappropriate to use perphenazine as a “fail-first” drug. In Phase 2, clozapine was remarkably effective and was substantially better than all the other atypical medications: 44% who received clozapine were able to stay on clozapine for the rest of the study. Unfortunately, clozapine is associated with serious side effects, including life-threatening blood and heart complications such as agranulocytosis (decreased white blood cell count) and myocarditis (inflammation of the heart); as a result, people who take clozapine must be monitored closely, which includes blood tests.

**What questions does CATIE leave unanswered?**

The preliminary results of the CATIE study looked solely at comparability among the medications regarding discontinuation, efficacy and side effects. There are many questions that analysis of the first two phases did not explore, including the following:

- Are certain subgroups of the participant population studied more prone to the side effects of these medications?
- To what extent is efficacy of any given medication affected by gender? By race/ethnicity?
- Were higher levels of clinical contact a factor in some participants' response to treatment?
- Was the provision (or absence) of support services a factor in some participants' response to treatment?
- Were there differences in the patient cadres at respective study sites that may have accounted for some of the results or that may inform clinical practices?
- According to the study authors, "Dose could have been a factor in the performance of the various agents studied," noting that the FDA-approved and commonly-prescribed dose ranges used in CATIE "may be below their optimal therapeutic doses."<sup>[10]</sup> Would the findings have been different if doctors and participants had explored higher dose ranges rather than choosing to switch medications?
- What is the effect on consumer outcomes of switching a medication?
- How will CATIE findings address newer atypical antipsychotic medications that were not part of the complete trial period?
- What are the implications for public policy affecting reimbursement and service access?

How should policymakers interpret CATIE results?

What decisions does CATIE support? What decisions cannot be made based on CATIE results?

**“ [CATIE] will provide valuable information to help physicians and patients choose the most appropriate medication for them. There is considerable variation among**

**individuals; what works for one does not necessarily work for another. It is important to have a variety of treatment options. The CATIE study provides specific information, on therapeutic effects as well as side effects, about those options.”**

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1. National Institute of Mental Health. September 2005. Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE). Available at: [http://www.nimh.nih.gov/healthinformation/catie\\_qa.cfm](http://www.nimh.nih.gov/healthinformation/catie_qa.cfm).
2. Initially, 1493 participants were enrolled in the study, but all data from one site (33 participants) was excluded due to concern about the integrity of data from that site.
3. Because of rounding, percentages may not add up to 100%.
4. Dry mouth, urinary retention, blurred vision, and constipation  
. Excessive drooling
6. Abnormally high amounts of white blood cells found in either the blood or in body tissues
7. An insufficient number of white blood cells
8. Inappropriate lactation
9. National Institute of Mental Health. September 2005. Questions and Answers About the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness Study (CATIE).
10. Lieberman, J.A. et al. 2005. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. *New England Journal of Medicine*, Vol. 353, No. 12, p. 1218.