

What CATIE Found: Results From the Schizophrenia Trial

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The authors provide an overview of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) sponsored by the National Institute of Mental Health. CATIE was designed to compare a proxy first-generation antipsychotic, perphenazine, to several newer drugs. In phase 1 of the trial, consenting patients were randomly assigned to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone for up to 18 months on a double-blind basis. Patients with tardive dyskinesia were excluded from being randomly assigned to perphenazine and were assigned to one of the four second-generation antipsychotics in phase 1A. Clozapine was included in phase 2 of the study. Overall, olanzapine had the longest time to discontinuation in phase 1, but it was associated with significant weight and metabolic concerns. Perphenazine was not significantly different in overall effectiveness, compared with quetiapine, risperidone, and ziprasidone. Also, perphenazine was found to be the most cost-effective drug. Clozapine was confirmed as the most effective drug for individuals with a poor symptom response to previous antipsychotic drug trials, although clozapine was also associated with troublesome adverse effects. There were no differences in neurocognitive or psychosocial functioning in response to medications. Subsequent randomizations suggest that a poor response to an initial medication may mean that a different medication will be more effective or better tolerated. Although the CATIE results are controversial, they are broadly consistent with most previous antipsychotic drug trials and meta-analyses; however, the results may not generalize well to patients at high risk of tardive dyskinesia. Patient characteristics and clinical circumstances affected drug effectiveness; these patient factors are important in making treatment choices. (*Psychiatric Services* 59:500–506, 2008)

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Although studies of second-generation antipsychotics in schizophrenia have indicated that these drugs are comparable to the first-generation antipsychotics in reducing psychotic symptoms and that they produce few neurologic effects, with the exception of clozapine, the evidence for their superior efficacy and safety has been inconsistent (1–10). As a result of dominant prescribing preferences for second-generation antipsychotics over first-generation antipsychotics, despite their greater cost, questions have been raised about the clinical advantages and the cost-effectiveness of the second-generation antipsychotics.

This article provides an overview of the primary outcomes of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which was supported by the National Institute of Mental Health and designed to compare the effectiveness of first- and second-generation antipsychotic medications (11–14). In this overview we review the design, methods, and results of CATIE, with a focus on the implications and limitations of the trial.

CATIE design and procedures

Design and measures

The rationale, design, and methods of CATIE have been previously described (11–14). The study was conducted between October 2001 and December 2004 at 57 U.S. clinical sites. Patients were randomly assigned to receive olanzapine, per-

phenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions and were followed for up to 18 months or until treatment was discontinued for any reason (phase 1) (Table 1). Patients with tardive dyskinesia (N=231, or 15% of the sample) were excluded from being randomly assigned to receive perphenazine and were assigned to one of the four second-generation antipsychotics (phase 1A). Ziprasidone was added to the trial after 40% of the patients had been enrolled. The initial randomization thus had four separate strata within which patients had an equal chance of being randomly assigned to the treatments: before ziprasidone was introduced to the study, patients with tardive dyskinesia would be randomly assigned equally to receive olanzapine, quetiapine, or risperidone; before ziprasidone was introduced to the study, patients without tardive dyskinesia would be randomly assigned equally to receive olanzapine, quetiapine, risperidone, or perphenazine; and after ziprasidone was added to the study, these same two groups would be randomly assigned equally to receive the same antipsychotics plus ziprasidone. If the phase 1 treatment was perphenazine, patients who discontinued perphenazine were then randomly assigned to double-blinded treatment with olanzapine, quetiapine, or risperidone (phase 1B). If patients in phase 1B again discontinued treatment, then they entered phase 2.

In phase 2, patients and their study doctor could choose between two randomization pathways. The "efficacy" pathway (phase 2E), recommended to individuals who discontinued the previous treatment as a result of inefficacy, compared open-label clozapine to double-blinded treatment with olanzapine, quetiapine, or risperidone. The "tolerability" pathway (phase 2T), recommended to individuals who discontinued the previous treatment as a result of intolerability, compared double-blinded treatment with olanzapine, quetiapine, risperidone, or ziprasidone.

Participants

Eligible patients were 18 to 65 years of age, had received a research diag-

nosis of schizophrenia, and were found to be able to take oral antipsychotic medication. Patients were excluded if they had a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a history of serious adverse reactions to the proposed treatments; had had only one schizophrenic episode; had a history of treatment resistance; were pregnant or were breast-feeding; or had a serious and unstable medical condition.

The study was approved by the institutional review board at each site, and written informed consent was obtained from the patients or their legal guardians.

Interventions

Identical-appearing capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), or perphenazine (8 mg). After January 2002 ziprasidone (40 mg) was added. The dosage of the medications was flexible, ranging from one to four capsules daily. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents. Patients had monthly study visits with the study physician and other research staff for clinical and research assessments, unless additional visits were needed.

General analysis approach

A consistent statistical plan for treatment group comparisons was generally applied across the studies involving CATIE data (13), although the approach to cost-effectiveness analyses (15) was somewhat different because of the focus on multiple phases of treatment. Analyses for phase 1 were conducted on four data sets with overlapping membership on the basis of the tardive dyskinesia and ziprasidone cohort stratification. Each data set included only patients with an equal chance of being randomly assigned to the treatments under comparison. Patients assigned to the perphenazine group, in particular, were compared only with patients who did not have tardive dyskinesia, and patients assigned to the ziprasidone group were compared with only other patients who were randomly assigned to groups after ziprasidone was added.

The primary comparison was an overall test between the four treatments available at the beginning of the trial, excluding patients with tardive dyskinesia and those randomly assigned to the ziprasidone group. If the overall test was significant at $p < .05$, then pairwise treatment group comparisons were conducted by using step-down testing and a Hochberg adjustment for multiple comparisons (16). Ziprasidone was separately compared with the other four drugs among patients randomly assigned to groups after ziprasidone became available, but patients with tardive dyskinesia were excluded from the perphenazine comparison.

The outcome measure of time until treatment discontinuation was evaluated by using survival analysis methods. Continuous outcome measures were evaluated at specific monthly intervals by using analysis of covariance (ANCOVA) and adjusting for relevant baseline characteristics at end of phase (by using ANCOVA with additional adjustment for a patient's duration in phase 1) and across all visits by using repeated-measures mixed models. Side effect event rates were evaluated by using Poisson regression, which accounted for a patient's duration in phase 1. Analyses in the studies using phase 2 data followed similar methods.

Published reports of CATIE findings

Initial phase 1 report

This initial phase 1 report evaluated the relative effectiveness of second-generation antipsychotics as compared with a first-generation antipsychotic, perphenazine (17). Only a minority of patients in each group remained on the assigned drug treatment for the duration of this study (discontinuation rates ranged from 64% to 82%).

Seventy-four percent of patients discontinued the study medication before 18 months (olanzapine, 64%; perphenazine, 75%; quetiapine, 82%; risperidone, 74%; and ziprasidone, 79%). The time to treatment discontinuation for all causes was longest with olanzapine, compared with quetiapine ($p < .001$) and risperidone ($p < .002$). The comparisons of olanza-

Table 1

Summary of outcomes of the Clinical Antipsychotic Trials of Intervention Effectiveness

Phase	Description	Main results
1 and 1A	A total of 1,460 patients with chronic schizophrenia considering a switch of antipsychotics or not currently taking an antipsychotic were randomly assigned to double-blind treatment with olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone; 1A included 231 people who had signs of tardive dyskinesia at study entry and were excluded from being randomly assigned to receive perphenazine	Olanzapine was significantly more effective than risperidone and quetiapine, as indicated by time to treatment discontinuation, with a similar trend favoring olanzapine over perphenazine and ziprasidone; olanzapine was associated with the greatest weight gain and the most adverse metabolic effects; no differences were found between drugs in effects on psychosocial functioning, symptoms, or quality-adjusted life-years; perphenazine was the most cost-effective because of lower drug costs
1B	A total of 114 patients who had been randomly assigned and then discontinued use perphenazine in Phase 1 were then randomly assigned to double-blind treatment with olanzapine, quetiapine, or risperidone	Olanzapine and quetiapine were significantly more effective than risperidone, as indicated by time to treatment discontinuation; trends showed that olanzapine was the most efficacious and that quetiapine was the best tolerated in this group who had discontinued perphenazine
2E	A total of 99 patients who had discontinued treatment with olanzapine, quetiapine, risperidone, or ziprasidone in one of the phase 1 studies were then randomly assigned to open-label clozapine or double-blinded treatment with olanzapine, quetiapine, or risperidone; 86% of patients stopped previous drug as a result of inadequate therapeutic effect	Clozapine was significantly more effective than quetiapine and risperidone, as indicated by time to treatment discontinuation; olanzapine was not significantly different than any other treatment
2T	A total of 444 patients who had discontinued treatment with olanzapine, quetiapine, risperidone, or ziprasidone in one of the phase 1 studies were then randomly assigned to double-blinded treatment with olanzapine, quetiapine, risperidone, or ziprasidone; 41% of patients stopped taking the previous drug as a result of inadequate therapeutic effect; 38% stopped taking the previous drug as a result of intolerable side effects	Olanzapine and risperidone were more effective than quetiapine and ziprasidone, as indicated by time to treatment discontinuation; trends suggested an olanzapine advantage among those who discontinued previous treatment as a result of inadequate therapeutic effect and a risperidone advantage among those who stopped taking the previous drug as a result of intolerable side effects; olanzapine was associated with the greatest weight gain and most adverse metabolic effects

pine with perphenazine ($p < .021$) and with ziprasidone ($p < .028$) produced similar results, but they did not meet the researchers' a priori standard of statistical significance, which adjusted for multiple comparisons. Times to discontinuation because of intolerable side effects or extrapyramidal effects for the treatments were not significantly different. Patients assigned to olanzapine had the longest time to discontinuation as a result of inadequate efficacy, the longest successful treatment time, and the fewest hospitalizations as a result of exacerbation of schizophrenia (Table 1). However, substantial increases in weight were more common with olanzapine, as were the largest adverse effects on hemoglobin A1C, total cholesterol, and triglycerides.

Neurocognitive outcomes

Keefe and colleagues (18) compared the neurocognitive effects in phase 1 among 817 patients who completed

longitudinal neurocognitive assessments. The primary aim was to delineate differences in the neurocognitive effects of these five treatments at the two-month assessment period. Neurocognition was slightly but significantly improved from baseline at each of the time points for all treatment groups. At two months, treatment resulted in small neurocognitive improvements of $z = .12$ for olanzapine ($p < .003$), $.23$ for perphenazine ($p < .001$), $.17$ for quetiapine ($p < .001$), and $.24$ for risperidone ($p < .001$), with no significant differences between treatment groups. For those who completed 18 months of treatment on the initially assigned medication, neurocognitive improvement was greater in the perphenazine group than in the olanzapine group ($p = .001$) and in the risperidone group ($p = .038$) but not in the quetiapine group. The ziprasidone group did not differ from any of the other treatment groups. Neurocognitive improvement predicted longer time to treatment discontinua-

tion, independently from symptom improvement, among patients treated with quetiapine or ziprasidone.

Keefe and colleagues (18) concluded that all of the antipsychotic treatment groups had a small but significant improvement in neurocognition; however, there was no difference between the groups after two months of treatment, and the improvements in neurocognition were not likely to be greater than placebo or practice effects.

Psychosocial functioning

Swartz and colleagues (19) evaluated whether improvement in psychosocial functioning was significantly different between phase 1 and phase 2 treatment groups. Psychosocial functioning was assessed by using the Quality of Life Scale (QLS). Although modest improvements were evident across treatment groups, there were no significant differences between treatment groups and there was no distinct superiority of any antipsy-

chotic in improving psychosocial functioning. Magnitude of improvement from baseline, based on within-group comparisons, was largely comparable at 12 months (average effect size .19 standard deviation units) for the olanzapine (.19), risperidone (.26), perphenazine (.19) and ziprasidone (.26) groups; improvement was somewhat less for quetiapine (.09), although gains for the quetiapine treatment group were more comparable with those in the other drug groups at six and 18 months.

Results were similar at six and 18 months, and there were no significant differences between the treatment groups in the amount of change in the QLS total score or subscales at six, 12, or 18 months. Patients treated with clozapine in the efficacy pathway made comparable gains. Early treatment discontinuations, especially among patients most impaired at baseline, limited the ability to achieve more substantial functional gains. More substantial improvements would likely require more intensive adjunctive psychosocial rehabilitation interventions.

Staying versus switching

Essock and colleagues (20) examined the impact of “staying versus switching” in phase 1 of the trial. Among patients who were randomly assigned to the olanzapine group or the risperidone group, those who were taking the same antipsychotic upon study entry had significantly longer times until discontinuation than did those who were taking different antipsychotics upon study entry. When these “stayers” were removed from the analyses, the original pattern of phase 1 results remained, although differences seen in the original analyses were attenuated. Essock and colleagues concluded that comparisons of medication effectiveness should take into account whether each of the medications being compared were newly started.

Cost-effectiveness

Rosenheck and colleagues (15) reported on the cost-effectiveness analyses of the trial evaluated from the perspective of each medication as a treatment initiation strategy and in-

cluding any subsequent antipsychotic medications used in phase 2 or 3 as part of that patient’s treatment trajectory. As a result these intention-to-treat analyses included all available observations, classified by initial drug assignment, and the costs of reassignment of most patients to another second-generation drug. The cost analysis included medications plus health services use. Quality-adjusted life years (QALYs) were assessed on the basis of Positive and Negative Syndrome Scale (PANSS) subscales (21) and side effect rating scales.

Although there was modest improvement over 18 months for all groups as measured by QALYs, there were no significant differences between perphenazine and any second-generation medication. Average total monthly health care costs were \$300–\$500 (20%–30%) lower for perphenazine than for second-generation antipsychotics, because of lower antipsychotic drug costs for perphenazine. There were no significant differences between treatments on QALYs, on the PANSS itself, or on three other measures of quality of life, and there were no differences when observations after phase 1 were excluded.

Rosenheck and colleagues (15) concluded that initiating treatment with perphenazine was less costly and no less effective than initiating treatment with each of the four second-generation antipsychotics as measured by the PANSS and by a disease-specific measure of QALYs that combined measures of symptoms and side effects.

Phase 1B outcomes

Stroup and colleagues (22) compared the effectiveness of the second-generation antipsychotics olanzapine, quetiapine, and risperidone among patients who had just discontinued the older antipsychotic perphenazine. The time to treatment discontinuation was longer for patients treated with quetiapine (median 9.9 months) and olanzapine (7.1 months) than with risperidone (3.6 months). There were no significant differences between treatments in the subgroups that discontinued as a result of inefficacy, intolerability, or

patient decision. Stroup and colleagues concluded that in a group of patients with chronic schizophrenia who had just discontinued the older antipsychotic perphenazine, the antipsychotics quetiapine and olanzapine were more effective than risperidone, as reflected by longer time to discontinuation for any reason. They concluded that the effectiveness and acceptability of antipsychotic drugs appear to vary considerably according to clinical circumstances.

Phase 2E outcomes

In the efficacy arm of phase 2, McEvoy and colleagues (23) compared the effectiveness of switching to clozapine versus another second-generation antipsychotic among patients who had discontinued treatment with a second-generation antipsychotic as a result of inefficacy in phase 1 of the trial. Ninety-nine patients who had just discontinued treatment with olanzapine, quetiapine, risperidone, or ziprasidone were randomly assigned to treatment with clozapine or another, newer second-generation antipsychotic not previously received in the trial. Time to all-cause treatment discontinuation was significantly longer for clozapine (median 10.5 months) than for quetiapine (median 3.3 months) or risperidone (median 2.8 months) but not for olanzapine (median 2.7 months). Time to discontinuation for inadequate therapeutic effect was significantly longer for clozapine than for olanzapine, quetiapine, or risperidone. At three-month assessments, PANSS total scores had decreased significantly more among patients treated with clozapine (–11.7) than among patients treated with quetiapine (–2.5) or risperidone (–4.1), although all decreases were modest. (Possible scores on the PANSS range from 30 to 210, with higher scores indicating greater symptom severity.)

The authors concluded that for patients with schizophrenia with inadequate response to a second-generation antipsychotic, clozapine was more effective than switching to another newer second-generation antipsychotic, although clozapine’s advantage was compromised by weight gain and metabolic sequelae.

Phase 2T outcomes

Stroup and colleagues (24) evaluated the primary outcome of time to all-cause discontinuation from the tolerability arm of phase 2. In phase 2T, 444 patients who discontinued phase 1 as a result of intolerability were randomly assigned to receive a drug that they had not previously received in the study—that is, olanzapine, quetiapine, risperidone, or ziprasidone. Although the intent of this phase was to evaluate patients who discontinued phase 1 as a result of intolerability, because there was a choice of which arm of phase 2 to enter, some patients and their doctors who had stopped the previous treatment as a result of inadequate efficacy chose this arm, presumably to avoid possible random assignment to clozapine.

The time to treatment discontinuation was longer for patients treated with risperidone (median 7.0 months) and olanzapine (median 6.3 months) than with quetiapine (median 4.0 months) and ziprasidone (median 2.8 months). Among the patients who discontinued the previous treatment as a result of inefficacy, olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine. There were no significant differences between treatments among those who discontinued the previous treatment as a result of intolerability.

The authors concluded that for patients who had just discontinued a second-generation antipsychotic medication, risperidone and olanzapine were more effective than quetiapine and ziprasidone, as reflected by longer time to all-cause discontinuation.

Implications of CATIE

The finding in CATIE that perphenazine was not significantly different in overall effectiveness compared with olanzapine, quetiapine, risperidone, and ziprasidone and the finding that perphenazine was the most cost-effective drug was a surprise to many observers. Although the CATIE results are controversial, the results of an earlier Department of Veterans Affairs Cooperative study (25), a recent study of second-generation antipsychotics from the United Kingdom (26), and a meta-

analysis of side-effects with low-potency antipsychotic drugs (4) are all broadly consistent with the results of CATIE, demonstrating no consistent overall benefits of second-generation antipsychotics.

The CATIE results also suggested that clinical circumstances affected drug effectiveness and that these circumstances may be useful in making treatment choices. Clozapine was confirmed as being the most effective drug for individuals with a poor symptom response to previous antipsychotic drug trials, although clozapine is encumbered by troublesome adverse effects. Olanzapine was consistently favorable in overall effectiveness and efficacy, but it was also consistently associated with adverse metabolic risks. Risperidone was consistently effective overall, combining good efficacy and tolerability. However, it was not as effective as clozapine for individuals who had stopped previous medications as a result of inefficacy, and it was not as effective as quetiapine among individuals who had just discontinued the first-generation drug perphenazine. Quetiapine, although similar in some ways to olanzapine in adverse effects, seemed to be a good choice for people who had discontinued perphenazine, and it was particularly well tolerated in this group, presumably because of substantial differences in drug action. Ziprasidone was consistently weight neutral and had the best profile of metabolic effects of all drugs studied in phases 1 and 2 of CATIE, although it was not generally efficacious in the dosage employed in the trial.

Several concerns about the design and implementation of the trial (27–29) are discussed below.

Tardive dyskinesia risk

The CATIE finding of no difference in tardive dyskinesia risk across treatment groups is of concern, because a lowered risk of tardive dyskinesia may remain an important advantage of second-generation antipsychotics and the study may have had limited power to detect new cases of tardive dyskinesia. For example, the older and chronic nature of the sample may have reduced the incidence of new cases of tardive dyskinesia. A re-

cent comprehensive review of past studies on tardive dyskinesia by Correll and colleagues (30) reported a 4.6% lower annual risk of tardive dyskinesia with second-generation antipsychotics, compared with first-generation antipsychotics, although the authors noted that the results could have been biased by the fact that all three head-to-head first- to second-generation comparison trials involved moderate to high doses of haloperidol. The CATIE finding of no difference in tardive dyskinesia risk across treatment groups is consistent with the findings of a meta-analysis of 31 randomized controlled trials, which found no greater risk of extrapyramidal symptoms between low-potency first-generation antipsychotics and second-generation antipsychotics other than clozapine (1). However, a finding of “no difference” could also be due to an inadequate design to detect new tardive dyskinesia cases or low statistical power. However, it is still possible that the advantages of second-generation antipsychotics in regard to extrapyramidal symptoms and tardive dyskinesia have been overstated or conflated with secular prescribing trends toward more moderate dosing of all antipsychotics.

Exclusion of tardive dyskinesia from the perphenazine group

The initial reason for excluding patients with tardive dyskinesia from random assignment to perphenazine was the belief in 2000 by senior scientific experts who provided input to the National Institute of Mental Health that patients with tardive dyskinesia should not be exposed to any first-generation antipsychotic. Within the non-tardive dyskinesia group (85% of the sample), patients had an equal chance of being assigned to each of the five available treatments.

It is argued that the exclusion of patients with tardive dyskinesia from assignment to perphenazine may have biased results by preventing perphenazine from being given to patients with more severe systems or patients who were treatment resistant. However, patients who had tardive dyskinesia at baseline were

not involved in any between-group comparisons involving perphenazine and second-generation antipsychotics. All perphenazine comparisons were limited to the non-tardive dyskinesia randomization strata, allowing unbiased comparisons. However, because the study weakly generalizes to patients at higher risk of tardive dyskinesia and because of the profound effects of perceived tardive dyskinesia risk on prescribing, some critics have suggested that the cost-effectiveness and other findings should be interpreted with caution (27).

Choice of dosing

Concern has been expressed that the mean modal dose of olanzapine was higher than in typical practice at the time of the CATIE study and that dosing of risperidone and ziprasidone were somewhat lower than in typical practice (28,29). Although drugs that were dosed higher than optimal might have had an advantage in terms of measures of effectiveness, those dosed lower would have a presumptive advantage in terms of side effects. Thus, any dose-related biases favoring effectiveness could have been offset by disadvantages in side effects. Although the possibility that other dosing regimens might have led to different conclusions cannot be ruled out, this uncertainty is no greater in CATIE than in any of the other flexibly dosed double-blind trials of second-generation antipsychotics.

Other concerns

The analysis by Essock and co-authors (20) regarding staying on an antipsychotic medication recently prescribed at baseline versus switching raises the specter that staying on one's pre-study drug may have offered an unfair advantage to more popular drugs, such as olanzapine and risperidone. However, that study suggests that the same superiority trends persist even after controlling for baseline drug regimen.

Conclusions

CATIE results have provoked strong reactions and extensive discussions among researchers, clinicians, con-

sumers, and policy makers. Because CATIE was large and independently funded, the results, in particular the "unexpectedly" good effectiveness and cost-effectiveness of perphenazine, have gotten a great deal of attention. Putting the results in context however, CATIE results are in fact quite consistent with other independently funded studies (25,26), meta-analyses (1-3), and other systematic reviews (10).

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