

CATIE phases 1 and 2 provide a compelling rationale for individualized treatment, which should be standard clinical practice for schizophrenia

WHICH ANTIPSYCHOTIC DO I CHOOSE NEXT?

CATIE phase 2 offers insights on efficacy and tolerability

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After nearly 3 out of 4 phase 1 patients stopped taking their assigned antipsychotics within 18 months, researchers in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) braced themselves for phase 2.^{1,2} In this phase, they sought answers to two challenges clinicians face when prescribing medications for chronic schizophrenia:

- What to do when response to an initial antipsychotic is inadequate.
- What to do when troublesome side effects emerge.

The researchers did not know how many phase 1 patients would sign up for another phase of the trial or which of the two medication pathways—efficacy or tolerability—they would choose. This article addresses what CATIE's phase 2 findings tell clinicians about “real-life” decision-making in schizophrenia treatment.

CATIE'S INITIAL FINDINGS

Funded by the National Institute of Mental Health (NIMH), CATIE is a three-phase, ran-

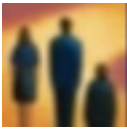


Table 1

Drug discontinuation patterns in CATIE phase 1

Measures	Findings after 18 months	
% of patients who discontinued medication for any reason	Olanzapine (64%) Risperidone (74%) Perphenazine (75%)	Ziprasidone (79%) Quetiapine (82%)
Time to discontinuation for any reason	Longest (most favorable) with olanzapine, but not statistically longer with olanzapine than with ziprasidone or perphenazine No statistical difference among risperidone, quetiapine, ziprasidone, and perphenazine	
Time to discontinuation for lack of efficacy*	Longer with olanzapine; no statistical difference among risperidone, quetiapine, ziprasidone, and perphenazine	
Time to discontinuation for intolerable side effects	No statistical difference among agents	
Rate of discontinuation for intolerable side effects	Highest (19%) with olanzapine (primarily because of weight gain or metabolic effects with this medication)	
Rate of discontinuation for extrapyramidal effects	Highest (8%) with perphenazine	
Rate of discontinuation for intolerability (overall)	Lowest with risperidone (10%)	

* Nonequivalent dosing in CATIE phase 1 is an ongoing debate.

domized, double-blind trial that began with 1,432 patients in phase 1. (For details on the study design, see the review by Nasrallah HA. CURRENT PSYCHIATRY, February 2006, p. 48-65.)

CATIE’s eligibility criteria are broad and include schizophrenia patients with comorbid conditions such as substance abuse and mood disorders. The primary outcome measure is all-cause treatment discontinuation, which incorporates efficacy, safety, tolerability, patient choice, and clinician choice (*Table 1*).

Phase 1 compared the efficacy and safety of four second-generation antipsychotics (SGA) and one first-generation antipsychotic (FGA).³ Nasrallah concluded that—despite the high discontinuation rate in that phase—there were “no winners or losers” among the five antipsychotics.

The results, Nasrallah concluded:

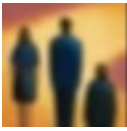
- provide a compelling rationale for clinicians to match medication profiles to individual patients
- support the need for clinicians to have choices among medications when treating patients with schizophrenia.⁴

WHAT TO DO NEXT?

When an initial antipsychotic proves inadequate or causes intolerable side effects, how do you choose a more efficacious or tolerable medication? Phase 2 offered CATIE patients and their clinicians two choices—an efficacy and a tolerability pathway (*Figure, page 33*).^{1,2}

Efficacy pathway. Patients who chose the efficacy pathway were randomly assigned to clozapine

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Table 2

Phase 2 efficacy pathway: Discontinuation for any reason

Measure	Clozapine	Olanzapine	Risperidone	Quetiapine
How many patients discontinued	25 of 49 (56%)	12 of 19 (71%)	12 of 16 (86%)	13 of 15 (93%)
Median time to discontinuation	10.5 months	2.7 months	2.8 months	3.3 months

(50%) or olanzapine, risperidone, or quetiapine.¹ Researchers selected clozapine as the major efficacy comparator because of its robust effects in treatment-refractory schizophrenia. Clozapine was given open-label because of its safety monitoring requirements; other treatments were double-blind.

As in phase 1, the primary outcome measure was time until discontinuation for any reason. Secondary outcome measures included time to discontinuation because of side effects, patient choice, or lack of efficacy.

Tolerability pathway. Patients who chose the tolerability pathway were randomly assigned to double-blind treatment with ziprasidone, olanzapine, risperidone, or quetiapine.² Ziprasidone was the major comparator because of clinical data showing a favorable tolerability profile.

The primary outcome measure was time to

discontinuation for any reason. Secondary outcomes included reason for discontinuation (as determined by the study clinician), symptomatic ratings, and evaluations of adverse effects.

Trial duration. No patients in either pathway received the same antipsychotics they had taken in phase 1. All patients could continue treatment through the 18 months of the CATIE trial or until they completed 6 months in phase 2.

EFFICACY PATHWAY RESULTS

Discontinuation. Consistent with literature about its efficacy in treatment-refractory schizophrenia, clozapine showed a robust clinical effect. Overall, more patients receiving clozapine stayed on treatment and for longer periods, compared with patients receiving olanzapine, risperidone, or quetiapine (Table 2).

On secondary measures, discontinuation for lack of efficacy was significantly lower with clozapine (11%) than with:

- olanzapine (35%)
- risperidone or quetiapine (each at 43%).

Discontinuation rates because of adverse effects or by patient choice were the same across all medications (Table 3, page 34). Patients on clozapine achieved better ratings in overall psychotic symptoms, positive symptoms, and general function, but not in negative symptoms.

Weight gain. On average, patients gained more weight while taking olanzapine (+1.1 lb/mo) than with:

- risperidone (+0.5 lb/mo)
- clozapine (+0.5 lb/mo)
- quetiapine (+0.5 lb/mo)

Differences in weight gain—or in metabolic

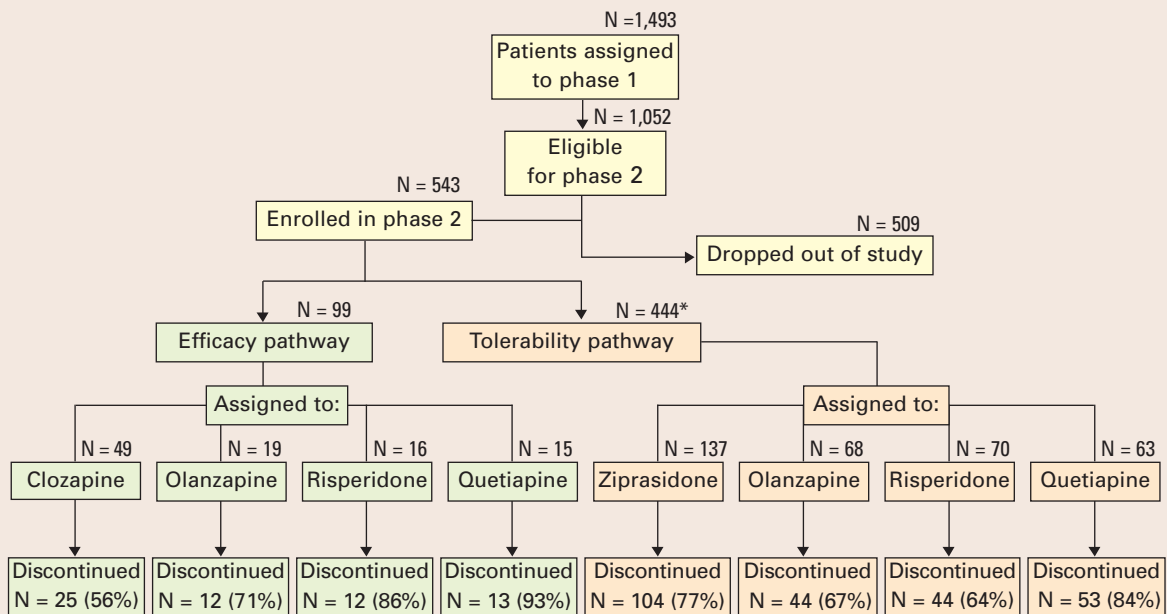
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Figure
CATIE phase 2: Distribution of patients in efficacy and tolerability pathways



N: number of patients

* 106 of the 444 patients were assigned before ziprasidone became available and were included in safety analyses.

parameters or other adverse effects—were not statistically significant, however.

TOLERABILITY PATHWAY RESULTS

Discontinuation. Patients in the tolerability pathway took olanzapine or risperidone significantly longer—median 6.3 and 7 months, respectively—compared with ziprasidone (4 months) or quetiapine (2.8 months).

- Time to discontinuation during phase 2 was the same across all drugs among patients who entered phase 2 because of intolerable side effects in phase 1.

- Time to discontinuation because of side effects also was similar whether patients discontinued phase 1 for lack of efficacy or intolerable

side effects. Patients stopped treatment in the efficacy and tolerability pathways for similar reasons (Table 3, page 34).

Weight gain. Patients taking olanzapine gained more weight (average +1.3 lb/mo) than did those taking the other drugs. Patients taking ziprasidone lost weight (average -1.7 lb/mo). Among 61 patients who gained weight during phase 1, 42% of those switched to ziprasidone lost weight in phase 2, as did:

- 20% of those switched to risperidone
- 7% of those switched to quetiapine.

Among those switched to olanzapine in phase 2, no one lost weight and 2% gained weight.

Metabolic effects. Some parameters changed, depending on drug assignment:

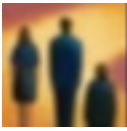


Table 3

Reasons patients stopped taking their medications in CATIE phase 2

Reason	Efficacy pathway	Tolerability pathway
All cause	69%	74%
Lack of efficacy	26%	29%
Lack of tolerability	10%	15%
Patient choice	26%	24%

- prolactin increased in patients switched to risperidone
- cholesterol and triglycerides increased in patients switched to olanzapine or quetiapine but decreased in those switched to risperidone or ziprasidone
- QTc interval measurements showed no difference across all drugs.

METHODOLOGIC CAVEATS

When considering how CATIE’s phase 2 findings might apply to clinical practice, keep in mind four caveats about the study’s design.

Clozapine was given open-label, yet quetiapine, olanzapine, and risperidone were given double-blind in the efficacy pathway. This pathway’s findings are consistent with what we know about clozapine and other SGAs in treatment-refractory schizophrenia, but how the open-label design affected clozapine therapy outcomes is unclear.

Were patients who knew they were taking clozapine more willing to “stay the course” than were patients in the pathway’s double-blind arm?

Discontinuation rates remained high. The 74% “overall discontinuation rate” in phase 1 surprised many psychiatrists because of the per-

ceived high rate at which patients did not adhere to the first medications they received. To some extent, the word “discontinuation” is imprecise, however, because this group includes patients who did not drop out of treatment altogether but chose to move on to phase 2.

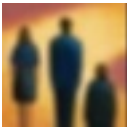
It is important to note, however, that nearly one-half of phase 1 patients who were eligible to enter phase 2 (509 of 1,052) did not. This group represents the true drop-out rate, which is substantial. The high rates of discontinuation seen in phase 1 also occurred in both phase 2 pathways (*Table 3*).

Few patients entered the efficacy pathway. In an approach designed to reflect routine clinical practice, the researchers recommended the efficacy pathway to patients who discontinued phase 1 because of lack of efficacy and the tolerability pathway to those who discontinued phase 1 because of intolerability. Many patients did not follow the recommendations, however, and seemed to choose their pathways based on whether they wanted a chance to receive clozapine or ziprasidone in phase 2.

Thus, among the 543 phase 1 patients who enrolled in phase 2, 99 (18%) entered the efficacy pathway, and 444 (82%) entered the tolerability pathway. The efficacy pathway included 85 patients who discontinued phase 1 for lack of efficacy and 5 for lack of tolerability. The tolerability pathway included 184 patients who discontinued phase 1 for lack of efficacy and 168 for lack of tolerability. **Dosages may not have been equivalent.** SGAs’ dosing equivalency is unknown,^{5,6} which impedes our ability to interpret comparative studies such as CATIE. The study’s designers developed the its dosing ranges by careful consideration, including recommendations from each SGA’s manufacturer.

Were patients who knew they were taking clozapine more willing to ‘stay the course?’

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Table 4

Mean modal antipsychotic dosages (mg/d) in CATIE phase 2 pathways*

	Clozapine	Ziprasidone	Olanzapine	Risperidone	Quetiapine
Efficacy pathway	332	—	23.4	4.8	642.9
Tolerability pathway	—	115.9	20.5	4.1	565.2

* 800 mg/d of quetiapine and 160 mg/d of ziprasidone are generally regarded as therapeutically equivalent to 20 mg/d of olanzapine.

As Nasrallah described,⁴ the trial’s dosages were not universally consistent with FDA-approved ranges or usual clinical practice (Table 4). In phase 2, for example, ziprasidone dosages were less than psychiatrists usually use, and quetiapine dosages were greater than usual.

Fortunately, studies are underway to determine each SGA’s optimum dosing. This work will help us understand what we can expect when we increase an antipsychotic’s dosage—a key step towards understanding dosing equivalency.

WHAT CLINICIANS CAN EXPECT

A recent analysis helps put CATIE’s findings in perspective. Citrome and Stroup⁷ quantified the results of phase 1 and 2 with respect to:

- number needed to treat (NNT)—how

many patients a clinician needs to treat with drug A to see one additional benefit, compared with drug B

- number needed to harm (NNH)—how many patients a clinician needs to treat with drug A to see a given adverse effect, compared with drug B.

Quetiapine’s dosages were higher than psychiatrists usually use; ziprasidone’s dosages were lower

In this analysis, the NNT for olanzapine (5.5 to 10) was lowest among the drugs compared in phase 1, and the NNT for clozapine (3) was lowest among those compared in phase 2. A lower number means that, overall, clinicians can expect a more robust treatment response.

On the other hand, the NNH for olanzapine in weight gain and metabolic disturbances (12.4 to 17.7) was the lowest in phase 1, indicating that clinicians can expect more weight gain and metabolic effects with olanzapine than with other SGAs. Ziprasidone had the highest NNH (106 to 208) among the agents in phase 2 for avoiding discontinuation because of weight gain or metabolic disturbances. In other words, ziprasidone appears less likely than other SGAs to cause metabolic problems.

These risk-attribution measures demonstrate the dilemma clinicians face when trying to match schizophrenia patients with antipsychotics.

Patients with schizophrenia who stop taking their medications because of inadequate response or side effects can benefit from switching to other antipsychotics. When selecting the next drug, evaluate your patient’s needs as well as the tolerability of the medication your are considering.

Bottom Line

CATIE was “an N of 1,493” subjects, whereas each patient we see in clinical practice is “an N of 1.” One patient may need a more-robust response; another may need improved tolerability.

We strive for balance, seeking to optimize efficacy—often by raising the dosage—while minimizing adverse effects.

WHAT TO TELL PATIENTS

CATIE phases 1 and 2 provide a compelling rationale for individualized treatment, which should be standard clinical practice for schizophrenia:

- All drugs used in phases 1 and 2 worked.
- All showed noteworthy adverse effects that were different for each drug.
- Different patients responded differently to each drug.

Using our clinical judgment and available information, we must match—as best we can—the individual patient’s characteristics with the antipsychotics’ risk:benefit profiles. CATIE phases 1 and 2 provide independent information on the comparative efficacy and tolerability of each medication.

The CATIE investigators and NIMH have done a great service to our field in providing a rich repository of timely information to inform clinical practice. But the CATIE study was not designed to answer all our questions about treating schizophrenia.^{8,9} Clinicians and patients need to look elsewhere for guidance on the roles of:

- psychosocial treatments
- recovery and the therapeutic alliance in maximizing outcomes
- long-acting SGA formulations
- aripiprazole (addressed in CATIE phase 3)
- SGAs in first-episode schizophrenia
- FGAs when a patient does not adequately respond to an initial SGA.

Related resources

- ▶ Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). www.CATIE.unc.edu.
- ▶ Lieberman JA. What the CATIE study means in clinical practice. *Psychiatr Serv* 2006;57(8):1075.

DRUG BRAND NAMES

Aripiprazole • Abilify	Quetiapine • Seroquel
Clozapine • Clozaril	Risperidone • Risperdal
Olanzapine • Zyprexa	Ziprasidone • Geodon
Perphenazine • Trilafon	

DISCLOSURES

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