The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project: Schizophrenia Trial Design and Protocol Development

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Abstract

The National Institute of Mental Health initiated the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) program to evaluate the effectiveness of antipsychotic drugs in typical settings and populations so that the study results will be maximally useful in routine clinical situations. The CATIE schizophrenia trial blends features of efficacy studies and large, simple trials to create a pragmatic trial that will provide extensive information about antipsychotic drug effectiveness over at least 18 months.

The protocol allows for subjects who receive a study drug that is not effective to receive subsequent treatments within the context of the study. Medication dosages are adjusted within a defined range according to clinical judgment. The primary outcome is all-cause treatment discontinuation because it represents an important clinical endpoint that reflects both clinician and patient judgments about efficacy and tolerability. Secondary outcomes include symptoms, side effects, neurocognitive functioning, and cost-effectiveness.

Approximately 50 clinical sites across the United States are seeking to enroll a total of 1,500 persons with schizophrenia. Phase 1 is a double-blinded randomized clinical trial comparing treatment with the second generation antipsychotics olanzapine, quetiapine, risperidone, and ziprasidone to perphenazine, a midpotency first generation antipsychotic. If the initially assigned medication is not effective, subjects may choose one of the following phase 2 trials: (1) randomization to open-label clozapine or a double-blinded second generation drug that was available but not assigned in phase 1; or (2) double-blinded randomization to ziprasidone or another second generation drug that was available but not assigned in phase 1. If the phase 2 study drug is discontinued, subjects may enter phase 3, in which clinicians help subjects select an open-label treatment based on individuals' experiences in phases 1 and 2.

Keywords: Randomized clinical trial, schizophrenia, antipsychotic drugs, effectiveness, longitudinal.

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The advent of the newer atypical or second generation antipsychotic medications developed in the wake of clozapine (olanzapine, quetiapine, risperidone, and ziprasidone) has raised considerable hope that treatments for schizophrenia will be more effective and better tolerated than in the past. The use of atypical medications has steadily grown, and this trend is expected to continue. However, there is no definitive evidence that these expensive medications can reduce morbidity and hospital use and improve community functioning, as compared to the conventional or first generation antipsychotic drugs.

The existing evidence regarding the relative effectiveness of first and second generation antipsychotics for schizophrenia is predominantly based on short-term studies and does not adequately address long-term effectiveness and cost issues. The studies of second generation antipsychotics to date, which have for the most part been sponsored by pharmaceutical companies and designed to achieve regulatory approval based on evidence of efficacy and safety, typically have lasted 4 to 12 weeks, have involved initially hospitalized patients with no medical or psychiatric comorbidities, and have permitted few concomitant medications. The main outcome measures of these studies have mainly been the core psychopathology of schizophrenia and well-known side effects (e.g.,

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extrapyramidal side effects [EPS]) that are particularly problematic for some of the first generation drugs. These studies have neither definitively demonstrated the "real world" effects of the newer atypical antipsychotics in the broad patient populations that receive them nor adequately examined the broad range of side effects that may occur. The limited types of assessment measures used and short study durations have not provided adequate information about treatment for this highly variable and chronic condition. Moreover, the patient samples involved in these studies and the conditions imposed by the restrictions of the protocols limit the generalizability of the results. Additional information is needed to inform clinicians about the appropriate role of atypicals. Because atypical antipsychotic medications represent a major budget item for health benefit plans, including State Medicaid agencies, objective information about their cost-effectiveness is direly needed by policy makers.

Consequently, as part of its public mental health care treatment initiative, the National Institute of Mental Health (NIMH) established a request for proposal (RFP) for a research program to evaluate the comparative effectiveness of antipsychotic drugs in disorders for which this class of drugs is indicated (RFP 99–DS–0001) (see Lebowitz et al., this issue). The RFP issued by the NIMH specified that the protocol should focus on atypical antipsychotic drugs and should follow a public health model. In particular, the RFP specified that the trial should do the following: focus on effectiveness and broader measures of outcome rather than efficacy alone; examine cost-effectiveness and the impact of external factors on treatment delivery, adherence, and outcomes; enhance generalizability by being as inclusive as possible, without exclusions for comorbid psychiatric disorder, drug abuse, or medical illness; place a premium on demographic and geographic diversity; use multiple types of treatment settings that generally represent the systems of care in which patients with schizophrenia are treated; and generate results that inform community clinical practice. In addition, the RFP called for the program to develop a network of sites and investigators able to respond to future needs for effectiveness research, to serve as a base for ancillary clinical investigations, and to include a mechanism for adding new antipsychotic medications in the future. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) program was funded through a contract awarded to the University of North Carolina (UNC).

This article describes the development of the study designed to assess the effectiveness of antipsychotic drugs for persons with chronic schizophrenia. (The article by Schneider et al. in this issue describes the development of the study designed to assess the effectiveness of antipsychotic drugs for persons with Alzheimer's disease with agitation and psychosis.) Soon after the contract period began in October 1999, the original group of investigators at UNC, Duke, and Yale expanded the Protocol Development Committee by including other schizophrenia researchers who were not part of the original team. The trial designs submitted in the contract application process were a starting point for the protocol development process. An initial day-long meeting of the committee took place in Chapel Hill, NC (November 1999), with subsequent weekly meetings held by teleconference. In this way, the protocol was developed by the CATIE team of investigators through an iterative, systematic process. Additional input was sought from various "stakeholder" groups, including consumer representatives, mental health care administrators, and policy makers.

In January 2000, a draft study design was presented to consumer representatives at an NIMH-convened workshop entitled Clinical Trials Recruitment: What Motivates People to Participate? Feedback from this meeting led to substantial protocol modifications. In March 2000, a revised draft protocol was submitted to the NIMH for review by its Scientific Advisory Committee for the CATIE program. This committee made additional recommendations that were incorporated into the final protocol.

Rationale for Trial Design

The CATIE schizophrenia trial addresses the aims of the CATIE RFP. It seeks to fill some of the existing gaps in translating efficacy to effectiveness. To do this, the study has adapted many of the characteristics of "pragmatic" randomized controlled trials (RCTs). Pragmatic RCTs aim to answer "real-life" questions of practical significance to clinicians and patients in real-world clinical settings (Hotopf et al. 1999). Such settings have varied levels of ancillary services and serve patients with comorbid psychiatric illnesses, general medical problems, and substance use disorders. Medication adherence is not ensured, as is the case in routine practice. However, such pragmatic studies randomize interventions and endeavor to ensure that treatments and the assessment of outcomes are blinded where possible.

The primary aim of the CATIE schizophrenia trial is to determine the comparative effectiveness of a representative conventional antipsychotic and the different atypical antipsychotic medications for a representative sample of patients seeking treatment for chronic schizophrenia as measured by all-cause treatment discontinuation rates and associated measures of effectiveness and safety. Potential causes for discontinuation include a clinical determination of inadequate therapeutic effect (efficacy failure) or unacceptable side effects (tolerability failure), patient inability or refusal to take the assigned antipsychotic (adherence/

compliance), and administrative reasons (e.g., subject moves out of the study area). Further, if differential discontinuation rates occur among the medications, the study is designed to identify key causes for discontinuation.

In the protocol development process, study design decisions were made by the Schizophrenia Protocol Development Committee with input from various "stakeholder" groups. Some of the key design decisions and their rationales are reviewed below.

Patient Sample. To make the results of the trial generalizable and representative of the broad group of chronic schizophrenia patients, there are few exclusion criteria. Patients with medical or psychiatric comorbidities and those who require concomitant other medications are included in the trial.

The patients who enroll in this study have chronic or recurrent schizophrenia. First episode patients and wholly treatment-refractory patients are excluded. First episode patients are excluded because of their high rates of response to antipsychotic medications at relatively low doses. Treatment-refractory patients are excluded because their severe illness may preclude detection of differential effectiveness that would be apparent in treatment-responsive patients.

A wide spectrum of patients with schizophrenia enroll in the study, ranging from partially remitted outpatients to exacerbated inpatients. Partially remitted patients, who have received benefit from antipsychotic medication but who remain symptomatic (because of lack of efficacy or inability to tolerate an efficacious dose) or who suffer significant side effects, commonly consider a change in medications. Patients whose condition is exacerbated also commonly need a change in medication. Patients who are seemingly doing well on their current medication but who wish to consider a change for reasons of greater improvement or better tolerability also enroll.

Inclusion of Conventional Antipsychotic Medications. This study offers an important opportunity to determine whether atypicals are indeed superior to conventional antipsychotic drugs. Perphenazine was selected as the conventional medication because it is a midpotency medication with only a moderate incidence of EPS (relative to high-potency medications and other midpotency medications) and sedation (relative to low-potency medications). We considered the appropriateness of assigning patients entering the study on atypical medications to a conventional antipsychotic. Because our aim of determining the relative real-world effectiveness of conventional and atypical antipsychotic medications is critical to clinicians and policy makers, we determined that only tardive dyskinesia (TD) is a contraindication for this treatment decision. Therefore, patients with TD are excluded from the arm of the study that allows random assignment to a conventional antipsychotic. In phase 1, patients with TD enter phase 1A, which includes randomization to only oral olanzapine, quetiapine, risperidone, or ziprasidone.

Long-acting intramuscular forms of conventional medications were carefully considered for inclusion in this study. A depot comparison gained strong support because of its clinical relevance for persons with a history of medication nonadherence or substance abuse, or with an unstable living situation. Ultimately, however, the following factors led to the decision not to include a depot comparison group in phase 1:

- The expectation that a depot form of an atypical medication would soon be marketed, limiting the future significance of our findings
- The difficulty of blinding injections and possible bias against the unblinded (or blinded) treatments
- The problem of testing a treatment indicated for patients with a history of medication nonadherence in a study that requires all patients to agree to take medications
- The expected difficulty of enrolling participants in a depot study with a conventional medication

Ultimately, we concluded that a comparison of oral to depot medications would not be a primary goal of this study and that the effectiveness of depot medications should be examined in a study primarily focused on that question.

Double-Blinded Treatment Conditions in Phases 1 and 2. The treatments in phases 1 and 2 are blinded (except for clozapine) to enable rigorous comparisons of treatment effectiveness between drugs. The rationale for blinding is sufficiently compelling despite the complications it introduces to the study's practical implementation and its ecological validity. Because the oral medications used in phases 1 and 2 have been marketed for several years, clinicians and patients have preconceived notions about the efficacy and side effect profiles of the medications. Therefore, oral medications are blinded and physicians, raters, and patients do not know which medication has been assigned to an individual. This is intended to decrease bias in ratings and biased decisions about treatment failure. Clozapine is open label because of the logistical complexities that blinding it would involve given the need for blood sampling for hematologic monitoring.

Patient and Clinician Involvement in Decision Making. In response to feedback from consumer and advocacy groups to an earlier version of this protocol at the NIMH-convened workshop mentioned above, it was decided to include participant input when determining possible treat-

ment options. Consumer advocates suggested that this feature would make the study more appealing to consumers and their family members and thus would improve enrollment and retention rates. When participants enter phase 2, they choose between two studies, one that compares clozapine to the other atypical medications not previously taken in the CATIE study, and another that compares ziprasidone to the other atypical medications not previously taken. In addition, subjects and their clinicians make a shared decision about an appropriate open-label treatment in phase 3. When a participant enters phase 3, partial information about phase 1 and phase 2 treatment assignments is given to the study clinicians and patients so that an informed treatment decision can be made based on previous experience in the study. The names of the phase 1 and phase 2 drugs are provided alphabetically rather than chronologically in order to help preserve the blind.

Augmentation With a Second Antipsychotic Medication. Simultaneous treatment with two antipsychotics is available in phase 3 as a result of feedback that the Protocol Development Committee received from numerous stakeholders, including several mental health care administrators and policy makers, who reported that combining antipsychotic drugs is a common treatment strategy when response to a single antipsychotic is suboptimal. We will obtain descriptive information about this treatment strategy because dual antipsychotic treatment is included as an option in phase 3. The results may help decide whether to include a two-antipsychotic arm in future CATIE trials.

Primary Outcome Variable. Time to all-cause treatment failure, marked by its discontinuation, was selected as the primary outcome variable. Although symptoms, side effects, functioning, costs, and so on are important outcomes, we chose treatment discontinuation as the primary outcome because it is a distinct measure that reflects both efficacy and side effects. All-cause treatment discontinuation is a clinically meaningful outcome that reflects the input of both the patient and the clinician. In the course of a patient's treatment, the need to change medications reflects the possibility that the treatment was not sufficiently effective or tolerable, or the belief that another treatment would be superior.

Guidelines ensure that physician-initiated treatment changes are made for only logical and justifiable reasons, so that each treatment to which patients are assigned is given every chance to be effective before a switch is made. Guidelines also are provided to help ensure that clinicians and patients attempt to optimize dosing and use adjunctive medications before determining that the drug is not useful or tolerable. The goal is for patients to be withdrawn from a study medication only when guideline-recommended treatment options have been exhausted and clear clinical deterioration persists, or for administrative reasons. Although participant retention is important, the safety and well-being of individual patients are the primary considerations in all clinical decision making.

Inclusion of Newly Approved Antipsychotics. Because of our desire that the CATIE trials be maximally informative regarding current clinical practice, we made contingency plans to include, if possible, new antipsychotic drugs that gained U.S. Food and Drug Administration (FDA) approval during the study's enrollment period. In February 2001, ziprasidone was approved by the FDA and was then added to phases 1, 2, and 3 of the study. In November 2002 aripiprazole was approved by the FDA and was then added only to phase 3 as an open-label treatment. Thus we expect information from randomized, blinded portions of the trial about ziprasidone, but will obtain only open-label, descriptive data about aripiprazole.

Methods

Specific Aims and Hypotheses. The specific aims of the schizophrenia trial are as follows:

- To determine the long-term effectiveness and tolerability of the newer atypical antipsychotics, *relative to perphenazine.* We hypothesize that treatment with the newer atypical antipsychotics is associated with greater long-term effectiveness and tolerability than treatment with perphenazine.
- To determine the comparative long-term effectiveness and tolerability of the newer atypical antipsychotics in adults with schizophrenia. We hypothesize that the newer atypical antipsychotics are similarly effective in treating psychopathology but have different side-effect liabilities.
- To determine, among patients who fail treatment with an initially assigned newer atypical antipsychotic, the long-term effectiveness and tolerability of the newer atypical antipsychotics, *relative to clozapine.* Patients with inadequate resolution of psychopathology, or marked sensitivity to EPS, are recommended to enter this phase 2 trial. We hypothesize that treatment with clozapine is associated with greater long-term effectiveness and tolerability than treatment with a newer atypical drug other than the one the patient initially received.

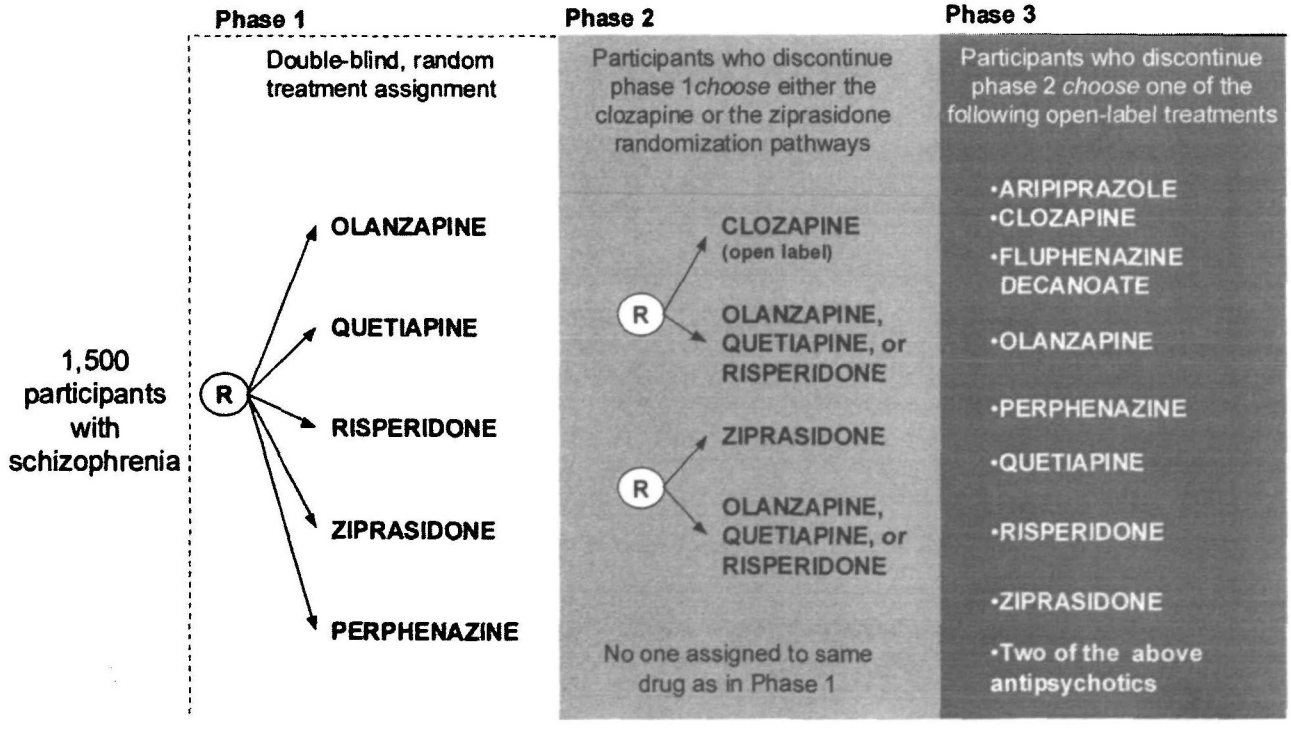
- To determine, among patients who fail treatment with an initially assigned newer antipsychotic, the long-term effectiveness and tolerability of the newer atypical antipsychotics, *relative to ziprasidone.* Patients with weight gain, hyperglycemia, or hyperlipidemia are recommended to enter this phase 2 trial. We hypothesize that treatment with ziprasidone is associated with greater long-term effectiveness and tolerability than treatment with a newer atypical drug other than the one the patient initially received.

Study Design. The CATIE schizophrenia trial is a multiphase RCT of antipsychotic medications involving up to 1,500 persons with schizophrenia followed for 18 months. Figure 1 contains a schematic diagram of the trial design. Participants are broadly representative of persons with the chronic and recurrent forms of schizophrenia. Patients are to be followed for at least 18 months. The study includes three treatment phases and a naturalistic followup phase. Persons who do well on an assigned treatment remain on that treatment for the duration of the 18-month treatment period. If an assigned treatment is deemed a failure, the patient moves to the next phase of the study to receive a new treatment. All study medications are double-blinded in treatment phases 1 and 2 except for clozapine, which is dispensed open label because of the clinical requirement to monitor maintenance of adequate white blood cell counts.

Outcome measures for the trial extend beyond efficacy and safety to capture more details about participants' quality of life, cognitive capacity, and use of general, mental health, substance abuse, and rehabilitative services. The representativeness of the subjects is ensured by recruiting into the trial a broad range of "real-world" patients, including those with comorbid conditions (e.g., substance use disorders, medical problems) that would exclude them from most clinical trials. The study is being conducted at sites that represent a broad array of clinical settings (e.g., State mental health, academic, Department of Veterans Affairs, health maintenance organization, managed care) in order to generate representative, generalizable, and practically relevant study findings.

In phase 1 of the trial, patients are randomly assigned to double-blinded treatment with oral perphenazine, olanzapine, quetiapine, risperidone, or ziprasidone. Patients with TD bypass phase 1 (and the risk of assignment to perphenazine) and are assigned to treatment with oral olanzapine, quetiapine, risperidone, or ziprasidone (phase 1A).

Figure 1. Schizophrenia trial design. Responders stay on assigned medication for duration of 18-month treatment period. Phase 1A = Participants with tardive dyskinesia are not randomized to perphenazine; phase IB = Participants who fail to respond to perphenazine are randomized to an atypical (olanzapine, quetiapine, or risperidone) before they are eligible for phase 2; R = randomized.



Participants who discontinue treatment with the conventional antipsychotic (oral perphenazine) in phase 1 are randomly assigned to double-blinded treatment with olanzapine, quetiapine, or risperidone (phase 1B).

In phase 2, participants who discontinue their assigned treatment with an atypical antipsychotic in phase 1, 1A, or 1B are recommended to one of two treatment assignment pathways based on their reason for discontinuation, as follows:

- The first pathway in phase 2 offers a 50:50 randomization to ziprasidone versus one of the other atypical antipsychotics (olanzapine, quetiapine, or risperidone) not previously received by the patient in this study. Patients who discontinued their previous treatment with an atypical antipsychotic because of intolerance to the previous regimen (e.g., weight gain) are expected to preferentially enter this study.
- The second pathway in phase 2 offers a 50:50 randomization to clozapine versus an atypical antipsychotic (olanzapine, quetiapine, or risperidone) not previously received by the patient in this study. Patients who discontinued their previous treatment with an atypical antipsychotic because of inadequate efficacy are expected to preferentially enter this study.

Phase 3 is for persons who discontinue the treatment assigned in phase 2. Research and clinical staff examine reasons for failure of the treatments assigned in phases 1 and 2. Based on this review, study treatment guidelines are reviewed and the research participant is followed in phase 3 on an open-label treatment chosen collaboratively by the clinician and patient.

The followup phase is for persons who are no longer willing to continue taking study medication or who have discontinued their phase 3 medication before 18 months from the time of initial randomization has elapsed. Followup phase participants are not provided with study medication but are followed naturalistically on their treatment of choice. Followup visits to collect basic outcome data are scheduled quarterly through 18 months from the time of a participant's initial randomization.

Subjects. A sample of 1,500 men and women, 18 to 65 years of age, who currently meet or have met in the past *DSM–IV* diagnostic criteria for schizophrenia, based upon the Structured Clinical Interview for *DSM–IV* (SCID; First et al. 1994), review of their clinical records, and input from available informants, are enrolled. Inclusion and exclusion criteria are listed in tables 1 and 2.

Treatments

Pharmacological treatments.

Dosing of study medications. Standard study capsules contain olanzapine 7.5 mg, quetiapine 200 mg, risperidone 1.5 mg, ziprasidone 40 mg, or perphenazine 8 mg (table 3). Clinicians can prescribe one to four capsules daily, based on individual patients' therapeutic response and side-effect burden.

Once and twice daily medication schedules. Quetiapine and ziprasidone require twice daily (BID) dosing, whereas perphenazine, olanzapine, and risperidone can be taken once daily (QD). Because it would deviate from clinical practice patterns to insist on BID dosing in all cases, we sought to minimize the number of patients who are required to take their medication BID, and still maintain blinding to the extent possible. Throughout the study, half of the patients randomized to perphenazine, olanzapine, and risperidone are assigned to BID dosing, and half are assigned to QD dosing. All quetiapine and ziprasidone patients receive BID dosing unless they are determined to need only one capsule per day.

Because quetiapine has a relatively slow recommended initial titration schedule, patients assigned to a BID dosing schedule begin their treatment using an initial dose strength and follow the titration schedule described in table 4. After the initial titration period using a starter pack of capsules, the total BID dose of all blinded study medications is identical to the QD dosing schedule. It is expected that there will be roughly equal efficacy and safety responses for the QD and BID dosing of these medications.

Dosing for open-label medications. As noted in table 5, the recommended dose range for open-label clozapine in phases 2 and 3 is 200 to 600 mg daily. The recommended dose range for fluphenazine decanoate injections available in phase 3 is 12.5 to 50 mg intramuscularly (IM) every 2 weeks for most patients. The recommended dose range for aripiprazole in phase 3 is 10 to 30 mg daily.

Transition to study medications. Because this study addresses long-term effectiveness and tolerability, not acute treatment efficacy, efforts are made to facilitate the transition of patients onto their study medications and prevent their destabilization by this process. For patients who are already taking an antipsychotic medication prior to any phase, tapering the previous medication over 2 weeks is recommended, but cross-titration is permitted for up to 28 days. Clinicians have substantial leeway in implementing these transitions according to clinical judgment.

Summary of pharmacological treatments. The methods allow double-blind comparisons among the newer atypical antipsychotics, and between the newer atypical antipsychotics and perphenazine. The blinding procedures allow dosing across commonly prescribed dose ranges of the study drugs (olanzapine 7.5–30 mg daily, quetiapine 200–800 mg daily, risperidone 1.5–6 mg daily, ziprasidone 40–160 mg daily, and perphenazine 8–32 mg daily) with equivalent numbers of capsules, that is, one to four daily.

Table 1. Inclusion criteria

1. Patients must be 18–65 years of age.
2. Patients must currently meet or have met in the past the *DSM–IV* criteria for schizophrenia.
3. Patients entering the study must, according to their own judgment in consultation with their physician, have a condition appropriate for treatment with an oral medication.
4. Patients must demonstrate adequate decisional capacity to make a choice about participating in this research study and must provide informed consent to participate.

Table 2. Exclusion criteria

1. Patients with a *DSM–IV* diagnosis of schizoaffective disorder, mental retardation, pervasive developmental disorder, delirium, dementia, amnesia, or other cognitive disorders are excluded.
2. Patients with well-documented, drug-related, serious adverse reactions to even one of the proposed treatment arms are excluded.
3. Patients in their first episode of schizophrenia are excluded. Patients will be considered to be in their first episode if they first began antipsychotic drug treatment for psychosis within the previous 12 months and have had psychotic symptoms for less than 3 years.
4. Patients with well-documented histories of failure to respond to even one of the proposed treatment arms are excluded. A treatment failure has occurred if the patient continued to demonstrate *severe* psychopathology in spite of fully adhering to treatment at an adequate dose of the medication for an appropriate length of time. Specific dose and duration criteria are as follows:
   - Olanzapine at dosages ≥ 30 mg/day for 6 consecutive weeks
   - Quetiapine at dosages ≥ 800 mg/day for 6 consecutive weeks
   - Perphenazine at dosages ≥ 32 mg/day for 6 consecutive weeks
   - Risperidone at dosages ≥ 6 mg/day for 6 consecutive weeks
   - Ziprasidone at dosages ≥ 160 mg/day for 6 consecutive weeks
5. Patients currently, or in the past, treated with clozapine *for treatment resistance* are excluded. Patients who have taken clozapine for reasons other than treatment resistance may be eligible.
6. Patients who are currently stabilized on haloperidol decanoate or fluphenazine decanoate and who require long-acting injectable medication to maintain treatment adherence are excluded.
7. Women who are pregnant or breastfeeding are excluded. Women of childbearing potential must agree to use appropriate contraception in order to enroll in this study.
8. Patients with tardive dyskinesia are excluded from assignment to conventional antipsychotic treatment arms.
9. Patients with a contraindication to any of the drugs to which they might be assigned are excluded.
10. Patients with a medical condition that is serious and acutely unstable are excluded.
11. Patients with the following cardiac conditions are excluded:
    - Recent myocardial infarction (<6 months)
    - QTc prolongation (screening electrocardiogram with QTc > 450 msec for men, QTc > 470 msec for women)
    - History of congenital QTc prolongation
    - Sustained cardiac arrhythmia or history of sustained cardiac arrhythmia
    - Uncompensated congestive heart failure
    - Complete left bundle branch block
    - First-degree heart block with PR interval ≥ 0.22 seconds
12. Patients on concurrent treatment with dofetilide, sotalol, quinidine, other Class Ia and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus are excluded.
13. Patients who have taken any investigational drug within 30 days of the baseline visit are excluded.

Table 3. Standard study dosing

Blinded medications	Dose per standard study capsule	Dose range
Olanzapine	7.5 mg	7.5–30 mg/day
Perphenazine	8 mg	8–32 mg/day
Quetiapine	200 mg	200–800 mg/day
Risperidone	1.5 mg	1.5–6 mg/day
Ziprasidone	40 mg	40–160 mg/day

Table 4. Initial twice-a-day dosing schedule

Blinded medications	Initial dosage capsules	Daily Dose (mg) During BID Titration				
		Day 1	Day 2	Day 3	Day 4 a.m.	Day 4 p.m.
Olanzapine	7.5 mg	7.5 QD	7.5 QD	7.5 BID	7.5	7.5
Perphenazine	8 mg	8 QD	8 QD	8 BID	8	8
Quetiapine	100 mg	100 QD	100 QD	100 BID	100	200
Risperidone	1.5 mg	1.5 QD	1.5 QD	1.5 BID	1.5	1.5
Ziprasidone	40 mg	40 QD	40 QD	40 BID	40	40

Note.—BID = twice a day; QD = once a day.

Table 5. Recommended dosing for open-label study medications

Open-label medications	Dose range
Fluphenazine decanoate	12.5–50 mg every 2 weeks
Clozapine	200–600 mg/day
Aripiprazole	10–30 mg/day

This design also allows comparison of QD versus BID dosing strategies.

Clinicians can adjust the dose of the assigned antipsychotic as clinically indicated within the range of one to four standard study capsules. Clinicians can prescribe adjunctive and concomitant medications whenever they believe these are indicated, but they must record the indications for their use. Antipsychotics other than the assigned study medicines are not allowed. The antipsychotic cannot be discontinued or changed without considering the treatment a failure. Additional antipsychotics may not be prescribed after cross-titration is complete except in emergencies or in phase 3 if patients elect the dual antipsychotic treatment option. The ongoing need for an additional antipsychotic is a criterion for treatment failure.

Psychosocial Interventions. Meta-analytic reviews (e.g., Mojtabai et al. 1998) support the additive effectiveness of psychosocial treatments delivered in combination with pharmacological treatment. Adding a psychosocial treatment produces greater improvement on measures of outcome than pharmacological treatment alone. The addition of a psychosocial treatment decreases relapse rates by 20 percent, on average, relative to medication treatment alone.

Research participants are offered psychosocial interventions directed at improving patient and family understanding of the illness, decreasing the burden of illness on the family, maximizing treatment adherence, minimizing relapse, enhancing access to a range of community-based rehabilitative services, and improving study retention. Interventions include the following:

- Patient and family education
- Opportunities for family support
- Adherence enhancement
- Broker/linking style case management or liaison with existing case management services

Patient and family education. All participants are offered an individually tailored educational plan adapted from the successfully implemented Texas Medication Algorithm Project (TMAP). The TMAP education plan is conducted in several phases and invites family participation if desired by the patient. Each phase involves one or more individual sessions, with patients moving to the next phase as appropriate. All sessions are presented orally, with supplementary print materials offered. Videotape educational presentations are also made available. To assess the intensity of educational efforts, research staff log the educational sessions provided to each subject.

The phases of the educational plan include the following:

- Individual introductory education. Content includes diagnosis, medications, and symptom self-monitoring.
- Individual followup. Content includes self-assessment of symptoms and side effects, assessing changes in symptoms, and so forth.

- Ongoing education. Content includes more extensive information about the illness, and treatment and reinforcement of earlier content.
- Group education/support. This phase offers opportunities for patients to discuss the illness with each other and provides referrals to other support groups.

Family support. Study sites are encouraged to work with the National Alliance for the Mentally Ill (NAMI) to facilitate offerings of family support groups at study sites or in the local community. Where feasible, structured family education programs (Journey or Hope/Family-to-Family program) are also offered.

Adherence enhancement. Kemp et al.'s (1996) compliance therapy intervention was adapted for CATIE to guide and enhance patient and family education on medication adherence. This cognitive behaviorally oriented approach equips therapists to address common problems with denial of illness and resistance to treatment. In the initial phase, the patient's stance toward treatment is elicited. In the second phase, ambivalence to treatment is explored, common misgivings are addressed, misconceptions are corrected, and indirect benefits of medications are emphasized. The third phase of compliance therapy focuses on treatment maintenance. Research associates and study clinicians have access to adherence enhancement materials on the CATIE Web site.

Case management. Sites vary in case management availability. Nonetheless, all participants have access to locally available community-based treatment and rehabilitative services so as to maximize potential rehabilitation and functioning. For subjects with active case management, study sites do not duplicate these services but serve as a liaison to ongoing case management services. Where subjects do not have case management provided, site personnel serve as broker/linking style case managers, attempting to gain entry for subjects to community services.

Measures and Assessment of Outcomes. Subjects attend monthly study visits for clinical examinations and to participate in assessments following the study's Schedule of Events (table 6). Outcome measures are obtained from a variety of sources, including patient self-report, clinician ratings, and ratings by trained study personnel.

Clinical and functional assessments.

Primary outcome. Time to all-cause pharmacological treatment failure, reflected by a decision to discontinue and change medications, is the primary outcome in the study. For time to withdrawal to serve as a meaningful variable, treatment retention must be maximized. Therefore, except under unusual circumstances, patients are withdrawn from the study only when treatment options have been exhausted and clear clinical deterioration persists. Nonadherence, exacerbation of psychopathology, or hospitalization do not necessarily require that a patient be withdrawn from the treatment that he or she is receiving in the study (e.g., if a patient experiences a recurrence of symptoms because he or she went away on a trip for 1 week and forgot to bring the medication and therefore did not take it). Similarly, only a side effect that produces significant subjective distress or objective dysfunction that cannot be resolved by dose adjustment or adjunctive medications should lead to treatment discontinuation. However, this focus on patient retention is balanced by the fact that the safety and well-being of patients are the primary considerations in all clinical decision making. Under no circumstances are patients maintained on their current study medications if there is a clear clinical reason to change or they prefer to move on to the next phase of the study or discontinue study medication or participation altogether.

In addition to this primary outcome measure, the clinical and functional outcome measures listed in table 7 are used to assess psychopathology, recovery, relapse, and severity of illness over the course of the study. Descriptions of these measures and the rationales for their selection appear in the article by Swartz et al. in this issue.

Side effects and adverse events measures. In addition to the measures listed in table 7, metabolic effects of the drugs are monitored regularly. Each participant's pulse, blood pressure, and weight are assessed regularly. To evaluate the effect of antipsychotic treatments on weight gain, glucose and lipid metabolism, waist-hip ratio (WHR), and body-mass index (BMI) are recorded regularly. In addition, fasting blood glucose level, hemoglobin A1C, lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), complete blood count, and serum prolactin level are collected according to the Schedule of Events (table 6).

Adverse events and side effects. Given the substantial clinical experience already available with these drugs, we elected to focus our monitoring on 18 well-known adverse events and side effects (AE/SE) that have been commonly reported with one or more of the study antipsychotics. By asking systematically about these 18 AE/SE, we will determine the relative frequencies and severities of these common and important AE/SE across the study antipsychotics. However, we also included a general inquiry section to record responses to questions about general physical health.

Family/caregiver experiences. Family burden is measured to assess the impact of schizophrenia on the objective and subjective burden on the family using a revised version of the Family Experiences Interview

Table 6. Schedule of Events

Schedule of Events

Interview	Screening	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	End of Phase	Phase 2/ Month 1	Phase 2/ Month 2	Phase 2/ Month 3
Screening Items																													
Randomization eligibility Form	X																												
Signed informed consent	X																												
Screening Sheet	X																												
Demographics	X																												
MOS Booklet	X																												
SCID/psychiatric history	X																												
Physical exam/medical history	X																												
Inclusion/Exclusion Forms	X																												
Review Inclusion/Exclusion criteria		X																											
General Health Rates																													
Follow-up ophthalmoscopic exam																										X			
Weight, waist, hip measurement, blood pressure and pulse	X		X		X			X			X			X			X			X			X			X			
Medical Diagnoses		X						X						X						X						X			
General Clinical Notes																													
HoCAT-Ch	X							X												X						X			
Concomitant/Adjunctive medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medication dispensing form, Drug accountability form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medication adherence form			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
General status (CGI-I, self-reported CGI, HAI, AIMS/DAI, habits, global satisfaction)		X	X	X		X		X			X			X			X			X			X			X			
PANSS		X	X		X			X			X			X			X			X			X			X			
Calgary Depression Rating Scale (CDRS)		X	X		X			X			X			X			X			X			X			X			
End of Phase form																										X			
Adherence, stressful/Side effects																				X									
Barnes Akathisia Scale		X	X		X			X			X			X			X			X			X			X			
Simpson-Angus EPS (modified)		X	X		X			X			X			X			X			X			X			X			
AIMS		X	X		X			X			X			X			X			X			X			X			
ACTH form		X	X		X			X			X			X			X			X			X			X			
Psychosocial Measures																													
Quality of Life (Heinrichs-Carpenter Quality of Life Scale, selected items from Lehman Quality of Life Interview)		X												X												X			
MacArthur Community Violence Instrument		X						X						X						X						X			
SF-12		X						X						X						X						X			
ITAQ		X						X						X						X						X			
Drug Attitude Inventory (DAI)		X						X						X						X						X			
SLUP-monthly		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SLUP-quarterly		X			X			X			X			X			X			X			X			X			
Family Experiences Interview Schedule		X						X						X						X									
Laboratory measurements																													
Pregnancy test (serum B-HCG)	X																												
Thyroid-stimulating hormone (TSH)	X																												
Prolactin	X				X			X						X						X						X			
Liver function tests	X				X			X						X						X						X			
Antipsychotic drug level					X			X			X			X			X			X			X			X			
Chemistry and Electrolytes	X				X			X						X						X						X			
Lipid Profile	X				X			X						X						X						X			
Hemoglobin A1C	X				X			X						X						X						X			
Fasting Glucose	X				X			X						X						X						X			
CBC	X				X			X						X						X						X			
Urinalysis	X																												
Urine Drug Screen	X				X			X			X			X			X			X			X			X			
Hair for Radioimmunoassay	X							X						X						X						X			
ECG	X		X																	X						X			X

Schedule of Events cont'd

Months	Screening	Baseline	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	End of Phase	Phase 2: Month 1	Phase 2: Month 2	Phase 3: Month 1
Neurocognitive Battery																													
WRAT-III Reading Test		X																											
Controlled Oral Association Test (Letter Fluency)		X		X				X												X								X	
Category Instances (Semantic Fluency)		X		X				X												X								X	
Maze		X		X				X												X								X	
Hopkins Verbal Learning Test		X		X				X												X								X	
Facial Expression Discrimination Test		X		X				X												X								X	
WAIS-R Digit Symbol Test		X		X				X												X								X	
Letter-Number Test of Working Memory		X		X				X												X								X	
Grooved Pegboard		X		X				X												X								X	
Computerized Continuous Performance Test		X		X				X												X								X	
Computerized Visuospatial Working Memory Test		X		X				X												X								X	
Computerized Wisconsin Card Sorting Test		X		X				X												X								X	

Note.—AE/SE = adverse events and side effects; AIMS = Abnormal Involuntary Movement Scale (Guy 1976); AUS/DUS = Alcohol Use Scale/Drug Use Scale (Kim et al. 1995); CBC = complete blood count; CGI–S = Clinical Global Impressions Scale–Severity; EPS = Extrapyramidal Side Effects; ITAQ = Insight into Treatment Attitude Questionnaire (McEvoy et al. 1989); MacCAT–CR = MacArthur Competence Assessment Tool–Clinical Research; PANSS = Positive and Negative Syndrome Scale (Kay et al. 1987); SCID = Structured Clinical Interview for *DSM–III–R*; SF-12 = 12-Item Short-Form Health Survey (Ware et al. 1996); SURF = Service Use and Resources Form; WAIS–R = Wechsler Adult Intelligence Scale–Revised; WRAT–III = Wide Range Achievement Test, 3rd edition. Visits 19–23, end of phase, phase 2/month 1, phase 2/month 2, and phase 3/month 1 only if required. Neurocognitive assessments must be done at final study visit for subjects completing the study.

Schedule (Tessler and Gamache 1995). Families and caregivers are asked about instrumental support provided, limit setting provided for disturbing behavior, time spent directly related to care for the patient, lost productivity, and financial contributions to the patient's care.

Medication adherence. Medication adherence is conceptualized as an intermediate outcome variable in this study. However, because adherence with treatment is a prerequisite for determining the effectiveness of the study medications as indicated by all other outcome measures, efforts are made to maximize participant adherence to medication regimens. Although these efforts to enhance adherence may confound the assessment of adherence as an outcome measure, relative to usual care, they do so equally across all treatment groups.

To enhance understanding of the relationship between patient attitudes toward medications, insight into illness, and medication adherence, we administer the Drug Attitude Inventory (Awad 1993) and the Insight Into Treatment Attitude Questionnaire (McEvoy et al. 1989) at intervals specified in the Schedule of Events (table 6).

A pill count is conducted monthly. The patient is asked a standard set of questions about medication adherence at each appointment. Study personnel synthesize the patient report, pill count, and any other available information into a global judgment of medication adherence.

Substance use. Substance use is examined in multiple ways. Subjects are asked quarterly about drug and alcohol use. Urine drug screens are performed quarterly. In addition, hair samples for radioimmunoassay to detect substances of abuse are collected during patient visits and shipped to a central laboratory for assessment.

Neurocognitive assessments. Because the choice of tests for a neurocognitive battery is often controversial, the tests were chosen with consensus approval from the leaders in schizophrenia and dementia research. A Neurocognitive Advisory Group was selected in concert with the NIMH project officer and the External Scientific Advisory Board. Selection of members was designed to ensure maximum consensus and integration of personnel across committees.

The neurocognitive battery is completed according to the Schedule of Events in table 6. The tests are listed below.

- WRAT-III Reading Test (Wilkinson 1993)
- Controlled Oral Word Association Test (Benton and Hamscher 1978)
- Category Instances (Category Fluency) (Benton and Hamscher 1978)
- Wechsler Intelligence Scale for Children–Revised, Mazes (Wechsler 1991)
- Hopkins Verbal Learning Test (Brandt 1991)

Table 7. Clinical and functional outcome measures

Psychopathology	Clinical Global Impressions Scale—Severity and self-report versions
	Positive and Negative Syndrome Scale
	Calgary Depression Rating Scale[1]
Adverse events/side effects	Barnes Akathisia Scale[2]
	Simpson-Angus Extrapyramidal Side Effect Scale[3]
	Abnormal Involuntary Movement Rating Scale
	Adverse events/side effects form
Psychosocial	Heinrichs-Carpenter Quality of Life Scale[4]
	Lehman Quality of Life Interview—selected items[5]
	MacArthur Community Violence Instrument[6]
	Medical Outcomes Study Short Form–12
	Insight Into Treatment Attitude Questionnaire
	Drug Attitude Inventory
Family experiences	Family Experiences Interview Schedule (adapted)

[1]Addington et al. 1990.
[2]Barnes 1989; Carpenter et al. 2000.
[3]Simpson and Angus 1970.
[4]Heinrichs et al. 1984.
[5]Lehman 1988.
[6]Steadman et al. 1998.

- Face Emotion Discrimination Task (Kerr and Neale 1993)
- Wechsler Adult Intelligence Scale–Digit Symbol Test (Wechsler 1974)
- Letter-Number Span (Gold et al. 1997)
- Grooved Pegboard (Lafayette Instrument Company 1989)
- Computerized Continuous Performance Test (Cornblatt et al. 1988)
- Computerized Test of Visuospatial Working Memory (Hershey et al. 1999)
- Computerized Wisconsin Card Sorting Test (Heaton et al. 1993)

These tests and the neurocognitive functions measured by them are described by Keefe et al. elsewhere in this issue.

Health services and cost-effectiveness assessments. External factors such as the contacts between the patient and his or her health care setting and psychosocial support system (including family interactions, living situation, environmental safety, and financial resources) may affect outcomes and also reflect the effectiveness of treatments. The methods used to examine the organizational context of care, the subject service utilization, and the basis for the study's cost-effectiveness and cost-benefit analyses in CATIE are outlined by Schneider et al. (2001) in an article describing the Alzheimer's disease trial and used by Rosenheck and colleagues elsewhere (Rosenheck et al. 1997, 1999). These methods are summarized here.

The high cost of atypical antipsychotic medications can be justified if their use leads to savings in other health care or non–health care costs or if they yield improvements in the well-being of patients, their families, or the communities in which they live. Cost analyses will be conducted from the perspective of society and will include the cost of medications and all other health care costs.

Costs will be measured as the product of the units of service × the cost per unit, and will be assessed through the Service Use and Resources Form (SURF; Rosenheck et al. 1998). The SURF comprehensively documents use of health services and non–health resource consumption such as involvement with the criminal justice system and public support payments. We will conduct a series of sensitivity analyses using different unit-cost estimates. Medication costs will be based on the specific dosing of all agents to each patient.

Effectiveness will be evaluated in two ways. First, we will use the utilities generated by the Health Utilities Index (HUI; Feeny et al. 1996), a health-related quality-of-life index that measures preference-based utilities and health states in quality-adjusted life years (QALYs). Second, we will combine other quality-of-life and symptom measures and scale them to generate disease-specific QALYs, using methods developed elsewhere (Rosenheck et al. 1998). Sensitivity analysis will be conducted using both measures of effectiveness.

Initially, costs and effectiveness measures will be examined separately. If the increased medication costs of

atypical antipsychotics are offset by reduced services costs, and outcomes are superior, then the atypical antipsychotics will emerge as dominant choices and further analysis will not be necessary. If both costs and benefits increase with atypical antipsychotics, further analysis will be undertaken using cost-effectiveness acceptability curves (Van Hout et al. 1994). These analyses take into consideration various estimates of the monetary value of a QALY and estimate the probability of achieving various cost-effectiveness ratios.

Safety

Serious adverse events, as defined by the FDA, are assessed according to FDA guidelines. Treatment-emergent adverse effects are monitored using the AE/SE measure described above.

Clinical Monitoring and Laboratory Tests. The schedule for clinical monitoring and laboratory testing appears in the Schedule of Events (table 6). Screening evaluations are intended to identify medical abnormalities and to establish baseline levels. Parameters to be monitored include clinical chemistry and electrolytes (sodium, potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, phosphorus, uric acid, calcium, total protein, albumin, creatine kinase, alkaline phosphatase), liver function tests, thyroid-stimulating hormone, complete blood count, urinalysis, fasting blood glucose, lipids (total cholesterol, HDL cholesterol, and triglycerides), urine pregnancy test (for all women), prolactin, and an electrocardiogram (ECG). Laboratory assessments are collected and processed via a central laboratory, while ECGs are processed through a central ECG laboratory.

Each patient's pulse, blood pressure, and weight are recorded at screening, month 1, and month 3, and quarterly thereafter. Height is recorded at screening. To evaluate the effect of antipsychotic treatments on weight gain, we calculate the WHR and the BMI on this same schedule. In addition to the screening ECG, an ECG is conducted at the month 18 visit, at each end-of-phase visit, and 1 month after a participant starts on a new study medication.

An ophthalmoscopic exam to evaluate for the presence of cataracts is conducted as part of the screening physical exam. Followup ophthalmoscopic exams are conducted every 6 months and at end-of-phase visits.

Statistical Methods and Analytic Plan

The statistical methods and analytic plan of the CATIE schizophrenia trial are described in detail by Davis et al. elsewhere in this issue. They are briefly summarized below.

Primary Outcome—Phase 1. The primary analysis will consist of a comparison of treatment discontinuation rates between the conventional treatment group and the pooled atypical treatment groups in phase 1 from the beginning of the trial (olanzapine, quetiapine, risperidone). Treatment discontinuation will be defined as withdrawal from randomized treatment or the study itself for any reason, including lack of safety, lack of efficacy, poor medication adherence, or patient decision (after clinical reasoning and discussion with the patient by the clinician have taken place). The analysis will be conducted on the intent-to-treat population, with success or failure defined for all patients randomized. The objective is to determine if the atypical treatments maintain patients on their original therapy for a longer period than the conventional therapy. To this end, Kaplan-Meier estimates of the time to treatment discontinuation will be produced. Hypothesis tests for assessing treatment differences will be based on the Wilcoxon rank test for differences in survival distributions (Kalbfleisch and Prentice 1980) between the pooled atypical treatments and the conventional treatment, adjusting for baseline status (exacerbated, partially remitted) and clinical site. Once daily and BID dose groups will be pooled for all primary analyses.

In the second step of the primary analysis, the three atypical treatment groups will be compared. Assuming a significant difference was found between the pooled atypicals and the conventional in phase 1, comparisons for time to all-cause treatment discontinuation will be made among the three atypical treatment groups for phases 1 and 1A combined to determine if any treatments are substantially different from the others.

All other analyses of the primary outcome or analyses of secondary outcomes will be considered descriptive in nature, and statistical significance will therefore be evaluated relative to $p = 0.05$ as a descriptive tool.

Secondary analyses of the primary outcome, controlling for baseline covariates, will be performed using proportional hazards regression models (Cox 1972). In particular, an analysis of treatment discontinuation adjusted for clinical site, baseline status, and whether the patient is randomized to a QD or BID treatment regimen will be conducted, and any interaction between baseline status or regimen and treatment will be assessed. Other covariates of interest will include baseline demographic variables (e.g., gender) and overall disease severity. Interactions between significant covariates and treatment effects will be assessed in the context of the proportional hazards models.

Primary Outcome—Phase 2. Patients are eligible to receive rerandomization to an atypical treatment (to which they had not previously been assigned) if their originally assigned atypical treatment fails. Because the second

stage treatment is randomly assigned among atypical treatment arms, the study design will support treatment comparisons based on this rerandomization. However, because patients and investigators will choose between two different trials in phase 2, data from these two trials will not be combined for statistical comparisons. Within each trial, analyses will be conducted with respect to selected outcomes in order to compare the performance of the different treatment groups as second lines of treatment. In particular, an analysis of time from re-randomization to all-cause treatment discontinuation will be conducted using survival analysis techniques as described above. The primary analysis will focus on two main hypotheses:

- Comparison of ziprasidone versus olanzapine, quetiapine, and risperidone combined in the trial for patients who discontinued the first randomized treatment because of tolerability issues
- Comparison of clozapine versus olanzapine, quetiapine, and risperidone combined in the trial for patients who discontinued the first randomized treatment because of lack of efficacy

Analyses will be performed using similar methodologies as those described for the first phase.

Other Outcomes. Initial analyses of all secondary outcome variables will be based on the phase 1 and 1A treatment randomization in an intent-to-treat fashion, regardless of the treatment the patient is receiving at the end of the study. The goal of this approach is to assess which treatment is superior as initial therapy regardless of any subsequent randomizations.

Human Subjects Considerations

Given the heightened public and scientific concern about the participation of mentally ill subjects in research, a CATIE Ethics Committee, chaired by Paul Appelbaum, M.D., was established to review all human subjects considerations. This committee reviewed the protocol and recommended the procedures outlined below.

Assessment of Decisional Capacity. All prospective research participants are screened for decisional capacity using the MacArthur Competence Assessment Tool–Clinical Research (MacCAT–CR) (Appelbaum and Grisso 1996). Persons who demonstrate adequate decisional capacity to participate in this research study are allowed to decide whether to enter the study. Those who choose to participate sign a consent form and enter the screening phase.

Persons who are initially assessed not to have the capacity to make an informed decision but who wish to participate are offered a brief structured educational program based on the one used by Carpenter et al. (2000). The program focuses on the prospective participant's difficulties in learning and manipulating information in an effort to improve the person's level of functioning to the point where a competent decision can be made about whether to enter the study. After this program is completed, decisional capacity is again assessed using the MacCAT–CR. Persons who demonstrate decisional capacity at that time sign a consent form and enter the screening phase of the study.

Persons who are determined not to have the capacity to consent to participate in a research study even after remediation are not enrolled in the study unless a guardian is available and guardian consent for research is allowed in the particular study site's jurisdiction.

To assess decisional capacity longitudinally, and to examine the effects of the study medications on decisional capacity, the MacCAT–CR is administered to participants at screening, month 6, month 18, and each end-of-phase visit. The screening, month 6, and month 18 administrations coincide with neurocognitive assessments.

Informed Consent and Subject Advocate Procedures. Consent is obtained at the outset for all phases of the study except for the followup phase. (Consent for the followup phase is obtained at the time of entry into that phase.) All participants are asked to appoint a person who serves as a "subject advocate," who is involved with the informed consent discussion and assists the subject with decision making. Optimally, the subject advocate is a person of the patient's choosing—usually a family member or close friend. In the event that such a person is not available, each research site designates a person not otherwise involved with the research project (e.g., a social worker, a case manager) to serve in this role. If at any subsequent point the participant is believed to have severely impaired capacities to protect his or her own interests, then the subject advocate makes a decision as to whether the patient should leave the study. That determination is based on whether there has been such a substantial decrement in the benefit-risk ratio for this participant that the assumptions on which the participant's original decision to enter the study were predicated are no longer valid. Involvement by the subject advocate is ongoing but is especially important at entry into phases 2 and 3.

Summary

This article has described the rationale, aims, and design of the CATIE schizophrenia trial; its procedures; and its

proposed method of evaluating the effectiveness of antipsychotic medications in the broad population of patients with schizophrenia who are treated clinically with them. The protocol represents a type of pragmatic trial that is intended to evaluate the effectiveness of treatments in the settings where they are used for the purpose of generating results that benefit clinicians, administrators, policy makers, and patients. In the context of clinical therapeutics and interventions research, such studies provide an important bridge for the verification and translation of findings from traditional randomized controlled trials to clinical practice and public mental health care.

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