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REVIEW

The CATIE Schizophrenia Trial: Results, Impact, Controversy

Theo C. Manschreck, MD, MPH, and Roger A. Boshes, MD, PhD

The CATIE (Clinical Antipsychotic Trials for Intervention Effectiveness) Schizophrenia Trial was designed to examine fundamental issues about second-generation antipsychotic (SGA) medications (olanzapine, risperidone, quetiapine, and ziprasidone)—their relative effectiveness and their effectiveness compared to a first-generation antipsychotic (FGA), perphenazine. This article reviews these and other findings from this important trial and offers a perspective regarding their meaning for practice and their significance for the advancement of research in psychiatry. The primary outcome measure, time to discontinuation, served as an index of effectiveness and was remarkably short; only 26% of subjects completed the 18-month trial on the medicine to which they were initially randomized. Subjects receiving olanzapine experienced a slightly longer time to discontinuation. Based on this single criterion, olanzapine showed greater effectiveness than the other agents despite its association with significant metabolic disturbance, especially weight gain. Perphenazine unexpectedly showed comparable levels of effectiveness and produced no more extrapyramidal side effects than the other agents. Despite modest prolactin elevation, risperidone was the best-tolerated medication. Ziprasidone was associated with weight loss and with positive impact on lipids and blood glucose. In Phase 2, clozapine demonstrated better effectiveness compared to other SGAs for subjects who discontinued their Phase 1 medication because of efficacy. Olanzapine and risperidone showed greater effectiveness in the tolerability pathway. CATIE secondary outcomes are currently being examined. Improvements in cognition were modest among all the agents in Phase 1, and perphenazine was no less effective in improving cognitive performance than the SGAs. Cost-effectiveness analysis revealed a significant advantage for perphenazine, due to the impact of the high-priced, brand-name SGAs on overall health care costs. (HARV REV PSYCHIATRY 2007;15:245–258.)

Keywords: antipsychotic drugs, cognition, cost-effectiveness, metabolic syndrome, schizophrenia

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INTRODUCTION

Treatment for schizophrenia entered a remarkable era in the 1950s. New neuroleptic medications, such as chlorpromazine, were widely administered and began to empty hospitals. Their serendipitous discovery led to a revolution in appreciating both the biological basis of the illness and the promise of somatic therapies. By the 1960s and 1970s, however, worries about tardive dyskinesia (TD), in particular, and extrapyramidal symptoms (EPS) dampened enthusiasm for neuroleptics. During the 1990s "conventional," first-generation antipsychotics (FGAs) were gradually replaced by a growing number of second-generation antipsychotics (SGAs), or "atypical" agents, which held the promise of reduced TD, EPS, and negative symptoms. Prescriptions for SGAs in the United States have now reached several billion

dollars in annual sales. Weight gain and other metabolic disturbances associated with the newer antipsychotics have alarmed the field. These concerns have been reinforced by epidemiological evidence that patients suffering from schizophrenia, independent of exposure to SGAs, experience generally poor health and shortened lives compared to the general population, especially for cardiovascular, infectious, and respiratory diseases.[1–3] Practitioners have started to question the newer agents: how do they compare to each other and the older conventional medicines, and are they worth the cost?

The National Institute of Mental Health (NIMH), acknowledging the strategic scientific and policy dimensions of these concerns, funded the CATIE (Clinical Antipsychotic Trials for Intervention Effectiveness) Schizophrenia Trial (57 U.S. sites; overall principal investigator, Jeffrey Lieberman, MD; organizing center, the University of North Carolina and Duke University), a large, double-blind trial that compared the effectiveness of five antipsychotics in the treatment of schizophrenia. These drugs included four atypical SGAs (olanzapine, quetiapine, risperidone, and ziprasidone, all introduced since 1994) and perphenazine (a medium-potency, conventional FGA available since the 1950s).

The primary questions addressed by the CATIE trial were: (1) How do SGAs compare to a representative FGA? (2) What is the comparative effectiveness of SGAs? (3) Are the SGAs cost-effective?

The CATIE trial consisted of three phases to examine these questions and others (see Figure 1).[5] The results of Phase 1 were published in September 2005.[5] In this article we discuss the principal results and other important findings from the first two phases of CATIE.

The CATIE trial has produced considerable data concerning the health and experience of a large sample of schizophrenia patients. Findings on substance abuse, occasional violence, occurrence of metabolic disorder, TD, cognition, and other clinical features illuminate various dimensions of schizophrenia and have considerable public health significance. While CATIE was not an epidemiologic study in the strict sense, these findings have broad implications for policy (particularly costs and the health impact of treatment itself) and for management of this disorder (such as which agents to use to initiate treatment, and when clozapine should be introduced).

Study Participants and Trial Overview

Fourteen hundred sixty adults with schizophrenia were studied for up to 18 months. Diagnoses were determined by Structured Clinical Interview for DSM-IV. The study was a pragmatic hybrid of efficacy and effectiveness trial designs.[6] That is, there was a double-blind, controlled element to the design, which involved the broad inclusion criteria and longer duration characteristic of effectiveness trials; both efficacy and effectiveness trials are essential for a fair evaluation of medication interventions.

Efficacy trials, usually sponsored by pharmaceutical companies seeking Food and Drug Administration (FDA) approval, attempt to establish efficacy and safety in controlled, relatively artificial, settings. Their aim is to determine

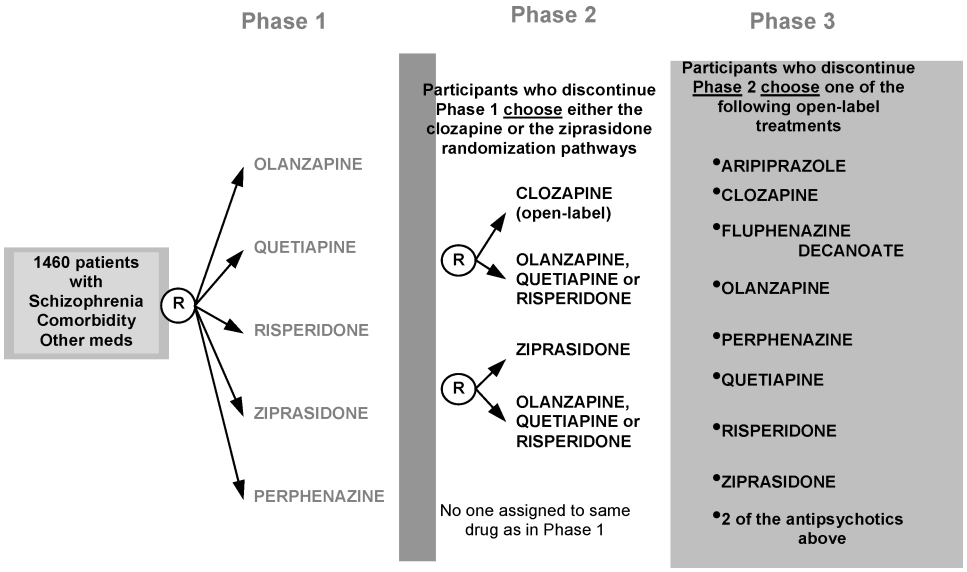

FIGURE 1. CATIE schizophrenia trial design. In Phase 1A, participants with tardive dyskinesia ($n = 231$) were not randomized to perphenazine. In Phase 1B, participants who failed perphenazine were randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for Phase 2. Source: Stroup et al. (2003).[4]

whether a drug works and whether it may cause specific side effects. Typically, these placebo-controlled, short-term trials involve relatively small samples, exclude comorbid conditions, often are conducted in inpatient settings where adherence is reinforced, restrict the use of other common medications, and utilize measures of side effects and psychopathology as end points. Less often, one or more alternative treatments known to have efficacy are compared. Such efficacy findings may not be widely applicable to outpatients with comorbid illness receiving concomitant medications.

Effectiveness trials attempt to emulate typical clinical conditions. They generally enroll large numbers from a variety of treatment settings in order to compare active treatments and to detect outcomes on a broad range of measures that have practical value.[6] The CATIE trial was specifically designed to deal with a sample of clinically heterogeneous patients, in the full range of practice settings for care of schizophrenia patients in the United States.[5] This focus made it possible to examine effectiveness, not simply efficacy.

Individuals enrolled in the CATIE Schizophrenia Trial met criteria for schizophrenia, the severity of which ranged from minimal to severe. Ages ranged from 18 to 65. Inclusion criteria allowed patients with comorbid medical, psychiatric, and substance abuse problems to participate in the study, consistent with "real world" design. Patients with first-episode schizophrenia were excluded in part because initial diagnoses are often unreliable. Patients were also excluded if they had a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders, as were those who were treatment resistant (defined as persisting severe symptoms despite adequate trials of one of the study medications or prior treatment with clozapine). Patients with severe or unstable medical conditions and pregnant women were excluded. Study participants provided written informed consent following discussion of the study and formal testing to demonstrate understanding of its elements.[4,7]

Trial Design and Measures

In Phase 1, participants were randomly assigned to double-blind treatment of up to 18 months either with one of the four SGAs or with perphenazine (see Figure 2). This design required that relative dose equivalencies be established in order to make meaningful comparisons of the agents—which meant, in turn, making certain assumptions about the doses. Whereas the maximum doses for olanzapine was 30 mg, which was higher than both the package insert suggestion and what many practitioners might consider, the maximum dose for risperidone was 6 mg, well below the upper range of clinical use.

In Phase 1A, patients with TD ($n = 231$) were excluded from random assignment to perphenazine because of its association with TD. Patients who discontinued perphenazine after initial drug assignment were rerandomized to double-blind treatment with olanzapine, quetiapine, risperidone, or ziprasidone (Phase 1b).

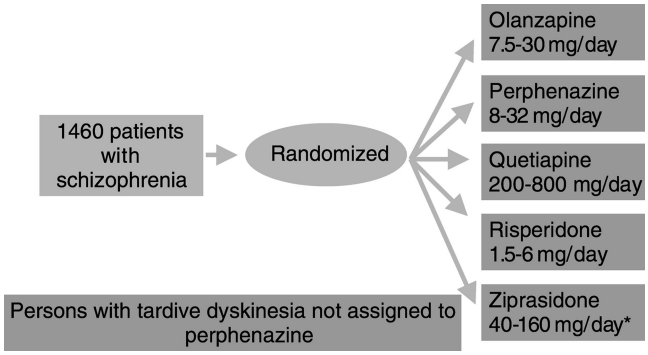

FIGURE 2. CATIE Phase 1: Practical trial: double-blind and randomized. Ziprasidone was added after 40% sample enrolled. Source: Stroup et al. (2003).[4]

If treatment in Phase 1 proved either ineffective or was not tolerated, participants could enter Phase 2 or discontinue the trial altogether. Participants who discontinued Phase 1 treatment due to inefficacy were encouraged to enter the Phase 2 efficacy pathway, which entailed either open-label use of clozapine or double-blind randomization to another SGA agent (olanzapine, quetiapine, or risperidone) not taken in Phase 1. The alternative approach for Phase 2 (tolerability pathway) was double-blind randomization of participants to either ziprasidone or to another atypical drug that they had not taken in Phase 1.

Phase 3 of CATIE was for individuals who did not do well on a Phase 2 treatment or who discontinued it. This phase involved open-label treatment with one of the following options: aripiprazole, clozapine, long-acting fluphenazine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or a combination of any of these drugs for patients willing to try another agent, with the choice of agent guided by the experiences of the two prior phases.

The primary outcome measure of the study was *all-cause treatment discontinuation*.[4,5,7] Staying on a drug treatment is critical to effectiveness (see Figure 3)—a brute fact that influenced the choice of this outcome measure. The assessment of efficacy in patients with schizophrenia is difficult given its protean symptomatology and impairments. A measure giving weight to the overall adjustment to treatment was proposed as a more meaningful measure than side effects or symptomatology ratings. Time to all-cause treatment discontinuation (see Figure 4) took into account the effect of treatment on symptom reduction, safety, and tolerability, as well as the clinician's and patient's judgments about efficacy and tolerability.

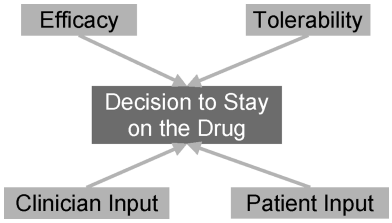

FIGURE 3. Drug effectiveness: Staying on the drug is critical. Source: Stroup et al. (2003).[4]

Specific reasons for discontinuation of treatment were assessed as key secondary outcomes, including failure due to inefficacy, intolerability, nonadherence, and patient decision. Other dimensions of schizophrenia examined as secondary outcomes included cognitive impairment, substance abuse, violence, treatment adherence, side effects, quality of life, and cost and use of services.

Dose ranges were based on U.S. practice patterns and consultation with the pharmaceutical companies that manufactured the study drugs. All antipsychotic medications were packaged in identical study capsules, which permitted dose titration using one to four capsules per day and ensured blinding of both investigators and subjects. Randomization of patients to ziprasidone treatment began after its FDA approval in early 2002, by which time some 40% of the CATIE subjects had already been enrolled. Plans for statistical analysis were accommodated to this difference in sample size. Clinicians were permitted to prescribe adjunctive medications except for antipsychotics. Psychosocial interventions were allowed throughout the treatment program.[4] Statistical analysis employed Kaplan-Meier survival curves to estimate the time to discontinuation of treatment for all intent-to-treat patients, and Cox proportional-hazards regression models to assess treatment differences with adjustments for site, baseline, and dosing strategy. Statistical adjustment (Hochberg) for multiple comparisons was included.[5]

PHASE 1 FINDINGS

Phase 1 examined 1460 intent-to-treat subjects. Their mean age was 40.6 years; 74% were male; and the mean duration of treatment prior to the study was 14 years. Median education was 12 years. Sixty percent were white, 12% Hispanic, and one-third African-American. Eighty-five percent were unemployed, and 59% had never married. Mean Positive and Negative Syndrome Scale (PANSS) at entry was 76, and mean Clinical Global Impression was 4—with both indices reflecting a moderate level of illness. Given that patients entering the study likely did so at least in part because of dissatisfaction with current treatment and that close to 60% of enrollees were taking one of the SGAs in the study (especially risperidone and olanzapine, and to lesser extent quetiapine), it seems reasonable to conclude that the typical CATIE patient was at least moderately ill, suggesting a high base rate of potential treatment resistance in this sample. While the sample was highly heterogeneous in clinical composition, the reasons for volunteering may have included some degree of dissatisfaction with current treatment (as already mentioned), remuneration for time and effort, altruism, or anticipation of added clinical attention. Phase 1 findings are summarized in Table 1.

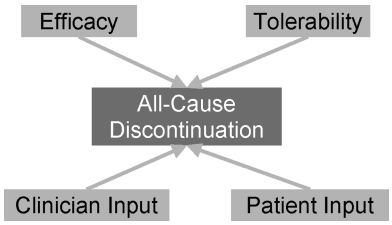

FIGURE 4. Primary effectiveness measure: All-cause treatment discontinuation. Source: Stroup et al. (2003).[4]

Seventy-four percent of subjects discontinued their treatment before the 18-month trial ended. Only 26% of patients remained on their initially assigned medication for the entire study (range, 18 to 36%). Discontinuation rate was lowest for subjects assigned to olanzapine (64%) followed by risperidone (74%), perphenazine (75%), ziprasidone (79%), and quetiapine (82%). The time to all-cause treatment discontinuation was significantly longer with olanzapine (median = 9.2 months) than with risperidone (median = 4.8 months) or quetiapine (median = 4.6 months). For perphenazine (median 5.6 months) and ziprasidone (median 3.5 months), the median time to discontinuation was shorter but, because of statistical corrections associated with smaller sample sizes, was not significantly different.

The rate of discontinuation due to lack of efficacy ($n = 340$, or 24% of the sample) was 15% for olanzapine (vs. range of 24 to 28% for all other drugs) and was statistically significant compared to quetiapine, risperidone, and perphenazine.

Rates of discontinuation because of intolerability ($n = 213$, or 15%) were statistically similar among the treatment groups, but risperidone showed the lowest (10%), and olanzapine the highest (19%), rates of discontinuation for this reason. The rates for the other three medications were 15%. The rate of discontinuation due to weight gain or metabolic changes was more than twice as great for olanzapine as for the other study medications (9% vs. 1% to 4%). Olanzapine caused significantly more weight gain than any of the other medicines, even after adjustment for duration of treatment. The average weight gain with olanzapine was 2.0 pounds per month. In addition, more patients in the olanzapine group reported gains of >7% of their baseline body weight—a common index of significant weight gain in clinical trials (30% versus 7% to 16%).[5]

TABLE 1. Results of CATIE Phase 1

	Dose range	*n*	Time to discontinuation (in months)	All-cause discontinution (% of entire cohort)	Reasons for discontinuation			
					Lack of efficacy	Intolerability	Patient's decision	Other
Olanzapine	7.5–30 mg	330	9.2	210 (64)	48 (15)	62 (19)	78 (24)	22 (7)
Perphenazine	8–32 mg	257	5.6	192 (75)	65 (25)	40 (16)	77 (30)	10 (5)
Quetiapine	200–800 mg	329	4.6	269 (82)	92 (28)	49 (15)	109 (33)	19 (7)
Risperidone	1.5–6 mg	333	4.8	245 (74)	91 (27)	34 (10)	101 (30)	19 (8)
Ziprasidone	40–160 mg	183	3.5	145 (79)	44 (24)	28 (15)	63 (34)	10 (7)

Source: Adapted from Lieberman et al. (2005).[5]

Olanzapine treatment was associated with elevations from baseline levels of cholesterol and triglycerides, fasting glucose (mean of 15.0 +/– 2.8 mg/dl) and glycosylated hemoglobin (.41 +/– .09%). In contrast, elevations in these measures were present, but considerably smaller, for perphenazine. Both risperidone and ziprasidone produced trends toward decreased triglycerides, and ziprasidone also showed reductions in glycosylated hemoglobin. Triglycerides were elevated among quetiapine users. Elevated triglyceride levels are often considered an index of insulin resistance, a key variable in the pathogenesis of diabetes. Increased prolactin levels, not related to symptom response, were present among risperidone users compared to those using other medicines, with a mean change from baseline of +13.8 ng/dl. Among the other agents, mean prolactin levels decreased, ranging from –1.2 to –10.6 ng/dl.[5]

Patients on perphenazine were more likely to discontinue because of EPS (8%), though it should be noted that EPS (Simpson-Angus scale) were not demonstrably higher with perphenazine. Predictor variables that were associated with an earlier time to discontinuation included longer time since the first use of an antipsychotic, the nature of the antipsychotic taken prior to entry in the study, higher baseline symptomatology (PANSS score), and younger age. Patients receiving olanzapine or risperidone prior to enrollment stayed in the study significantly longer than those who had taken no antipsychotics or had taken a combination treatment or single agent other than olanzapine, quetiapine, or risperidone. There were no significant differences in the percentage of patients who experienced movement disorders (Abnormal Involuntary Movement Scale severity, akathisia, or EPS).

Rates of discontinuation due to patient decision ($n = 428$, or 29.9%) ranged from 24% to 34%, reflecting a substantial role in the effectiveness equation. Unfortunately, the reasons for discontinuation were not determined in the trial; these data might have had value in understanding the participants' perceptions regarding the trial's design and what to expect, as well as their specific reactions to the agents they received.

While baseline scores were in the moderate to severe range, total PANSS responses improved for all groups during the trial, with no substantial differences among drugs. These results suggest that prescreening successfully excluded the most treatment-resistant subjects.

Individuals who received olanzapine were less likely to be hospitalized for an exacerbation of schizophrenia compared to those in the other four groups (11% vs. 15% to 20% for other drugs). Duration of successful treatment (defined as a Clinical Global Impression of Severity score of either mildly ill or better, or moderately ill after improvement of more than 2 points from baseline) showed a median of three months for olanzapine compared to approximately one month for the other medications.

Overall, olanzapine was more efficacious than the other drugs but was also associated with significant weight gain and metabolic change. The FGA perphenazine was as effective as three of the SGAs and as well-tolerated.

PHASE 2 FINDINGS

Phase 2 examined a smaller number of subjects who had completed Phase 1 and, because of either lack of efficacy or intolerability of the side effects, elected to enter Phase 2 for a second randomized trial.[8–10] The real-world design empowered the subjects to have a say in selecting these options, and many decided against the clozapine arm (efficacy pathway). Rather, they chose another SGA for this phase of the study. Those results were published in 2006.[8,9]

As a result the Phase 2E (efficacy, or clozapine, pathway) trial had 99 subjects, whereas Phase 2T (tolerability, or ziprasidone, pathway) attracted 444 subjects. Phase 2T subjects were randomized to one of four SGAs. The clozapine pathway involved randomization to either open-label treatment with clozapine or double-blind assignment to an SGA not received in Phase 1. Subjects in the clozapine pathway were younger, more likely to be male, more likely to have entered CATIE with more than four prior psychiatric hospitalizations, and to have had higher scores on baseline

PANSS and Clinical Global Impression.[8,9] In other words, they tended to be sicker than other groups of patients.

Phase 2T turned out like Phase 1, with high rates of discontinuation for all causes: 74%. Risperidone (64% discontinuation; median = 7 months) and olanzapine (67% discontinuation; median = 6.3 months) were more effective than quetiapine (84% discontinuation; median = 4 months) and ziprasidone (77% discontinuation; median = 2.8 months). Risperidone was most effective for Phase 1 patients who switched for tolerability reasons. Olanzapine proved most effective in Phase 1 patients who switched for efficacy reasons. The lowest rate of metabolic problems was associated with ziprasidone. Phase 2T established that olanzapine was slightly more efficacious than the other agents, but weight gain and other metabolic side effects limited the advantage of overall effectiveness. Risperidone had a better balance of tolerability and efficacy, particularly among those patients who had previously experienced tolerability problems.[8] Perphenazine was not an option in either of the Phase 2 pathways. In retrospect, given perphenazine's effectiveness, the decision to exclude it was unfortunate (the decision was made because the study's primary goal was to compare the SGAs with each other).

The results for the Phase 2E (the efficacy pathway) were noteworthy. The rate of discontinuation for all causes favored clozapine (56% versus 71% to 93% [the range for the other agents]). Treatment discontinuation was 10.5 months (vs. range of 2.7 to 3.3 months for olanzapine, risperidone, and quetiapine). Clozapine-treated individuals had a more robust resolution of psychotic symptoms during Phase 2, but this advantage was partially offset by substantial metabolic complications.[9]

Phase 3 results have not yet been analyzed.[10]

OTHER FINDINGS

The primary intention of the CATIE study was to determine whether the SGAs offer any definitive clinical and public health advantages over FGAs. Other rationales for undertaking the study included the assessment of side effects (particularly weight gain and other metabolic effects) and costs.

Metabolic Syndrome

Patients with schizophrenia have a higher risk for weight gain and other metabolic abnormalities associated with the metabolic syndrome (MS) (see text box) and for both diabetes and cardiovascular disease in comparison to the general population.[2,3,12] MS, for example, is associated with a three-fold increased risk for coronary artery disease and stroke.[13] Progression to diabetes for MS individuals is common. SGAs may also contribute to metabolic side effects that further increase the cardiovascular risk in treated patients.

Metabolic Syndrome Criteria
(>3 Risk Factors Required for Diagnosis)

Risk factor	Threshold
Abdominal obesity	Waist circumference
Men	>40 inches (>102 cm)
Women	>35 inches (> 88 cm)
Triglycerides	>150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>130/85 mm Hg
Fasting glucose	>110 mg/dL

Source: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002).[11]

According to one report, diabetes risk in schizophrenia patients increased approximately at the same rate as in the general population prior to 1995.[2] However, between 1996 and 2001, risk in schizophrenia accelerated, with an estimated 3.1% of the total 10% prevalence attributed to SGA drug use.[14] The overall effectiveness of these agents for the management of schizophrenia therefore is compromised by side-effect profiles, particularly side effects that have an impact over extended periods of time. Furthermore, intolerable side effects are known to reduce adherence to medication, leading to relapse.

The CATIE findings regarding efficacy and metabolic effects of the five agents are important in themselves, but baseline assessments of metabolic features in patients with schizophrenia are also noteworthy. Fasting glucose and lipid measurements were collected at baseline from 689 subjects of the 1460 patients recruited for the study. A comparative analysis was performed using a randomly selected sample from the Third National Health and Nutrition Examination Survey (NHANES-3), matched one-to-one on the basis of gender, age, and race/ethnicity.[15] Female gender, increased age, and non-Caucasian ethnicity were associated with higher rates of MS. Matching on socioeconomic status, also associated with MS, was not completed. CATIE males were more likely to have MS than NHANES males (36% vs. 19.7%), and CATIE females were more likely to have MS than NHANES females (51.6% vs. 25%). This increased risk was present even after statistically controlling for the higher body mass indexes in the CATIE subjects, with CATIE males having 85% greater likelihood, and CATIE females 137% greater likelihood, of MS than their matched NHANES controls. In other words, weight itself was not a sufficient factor to account for these risk differences.

Baseline CATIE data confirmed previous reports that individuals with schizophrenia are at a significantly higher

metabolic and cardiac risk than the general population. A considerable percentage of the CATIE study participants presented with diagnoses of hypertension (20%), diabetes (11%), and dyslipidemia (14%) at baseline.[5] Prevalence of MS in study participants (42%) indicated that a significantly greater proportion of females carried that diagnosis (51.6% for females vs. 36% for males).[12,15]

A clinical comparison of CATIE subgroups with and without MS indicated increased somatic concerns and physical impairment scores on a health status assessment among those with the syndrome.[12] The two groups did not differ with respect to cognition, quality of life, symptom severity, or depression. Antipsychotic exposure and self-reported substance and alcohol abuse were not predictors of MS, but age, race, and ethnicity were significant predictors.[12] In addition, an observation from baseline CATIE results highlighted that those patients with treatable metabolic conditions were not receiving medical treatment. Sixty-two percent of CATIE patients with hypertension, 89% with dyslipidemia, and 45% with diabetes were not receiving medical treatment.[16]

Cognition

We now appreciate that cognitive dysfunction is a key disabling characteristic of schizophrenia, but efforts to characterize this dimension of the disorder have long been plagued by methodologic and specification problems. Moderate to severe cognitive difficulty is present in virtually every patient with schizophrenia.[17] Over and above the psychotic symptoms or pharmacological side effects that can impair cognitive activity in schizophrenia, the disease itself produces a persistent disturbance in cognition. This dimension of the disorder is frequently thought of as a domain of neuropsychological impairment, most commonly referred to as neurocognition. Neurocognitive compromise has been recognized as the major determinant of real-world functioning and of prognosis for treatment. Impaired cognitive performance is critical to understanding the severity of schizophrenic compromise and must be an essential treatment target in treating patients with schizophrenia.[17,18]

The CATIE trial, in addition to providing baseline data and follow-up on cognitive function, was designed to eliminate methodological shortcomings that characterized previous studies regarding the impact of SGAs on cognition.[19] Many earlier studies were nonrandomized; many used excessive doses of the typical comparator medication; and some of the study samples were small. All too often, fundamental questions about whether cognitive improvement was secondary to symptom improvement or simply represented the impact of reduced side effects, such as anticholinergic effects, were not adequately addressed.

The baseline assessment of cognitive functioning in CATIE evaluated neurocognitive performance as well as the relationship of cognitive deficits to symptoms. CATIE examined a number of cognitive domains, including processing speed, reasoning, verbal and working memory, vigilance, and social cognition.[17,19] Baseline data were summarized by calculating a composite neurocognition score for each subject. This score accounted for a substantial portion of the variance of the cognitive measures, suggesting that it adequately captured the cognitive compromise in the schizophrenic subjects. Neurocognitive deficits (reflected in this score) were modestly correlated with negative symptoms ($r = 0.13$ to 0.27), but correlations with positive symptoms were almost nil ($r < 0.08$).[17] The severity of the impairments was similar to that described in prior meta-analyses: a broad cognitive deficit characterizes the entire cohort of patients with schizophrenia.

In CATIE, the evaluation of relative effects of antipsychotics on neurocognitive performance at 2-, 6-, and 18-month follow-up periods showed that all of the treatment groups had small improvements in performance, but there were no significant differences among the groups.[19] Neurocognitive change was found to contribute, for some antipsychotics, to overall effectiveness (as measured by time to discontinuation). After 18 months an estimate based on a more limited testable sample showed evidence of incremental improvement in cognition that favored perphenazine over the other treatments ($p < .05$). The results indicated, however, that most of the improvement occurred during the first two months of treatment. Individuals who had anticholinergic medications added during the first two months of the trial showed a mild worsening of cognition. Individuals who did not receive anticholinergic medication showed a .18 standard deviation enhancement of the mean cognitive composite score.

One possible interpretation of these data is that the cognitive benefits previously claimed for the SGAs may have been realized already among the 60% of CATIE recruits who were receiving SGAs prior to enrollment. Hence the trial could do little to improve individual performance. This interpretation must be tempered, however, by the evidence that perphenazine performed as well or better than the SGAs and that statistical analyses designed to ferret out such possibilities showed no such effect.

The important conclusions of the CATIE trial are that cognitive impairment is present in almost all patients with schizophrenia and is highly correlated with impaired functional outcomes.[17,19] While previous studies had concluded that SGAs provide modest cognitive benefit over FGAs (particularly haloperidol), CATIE data disputed these findings; there were no differences in the modest cognitive improvements achieved with all the treatments, including perphenazine.[20,21]

Tardive Dyskinesia

The CATIE baseline data examined those individuals identified at the outset as having TD. The 231 patients with TD were older (by approximately eight years), had received antipsychotics for much longer than other study participants, and were more likely to be receiving a conventional neuroleptic and an anticholinergic agent at baseline. There was no evidence that diabetes or hypertension predicted TD. Substance abuse was a predictor. Patients with TD did not have poorer cognition but did have higher ratings of psychopathology, akathisia, and EPS compared to their peers.[22] These findings support a hypothesis proposed by Timothy Crow[23] in 1982. Almost a century earlier, Emil Kraepelin described abnormal motor activity among unmedicated patients with schizophrenia that was identical to the movements associated with TD.[23] Crow proposed, in contrast to the conventional view that TD results from antipsychotic drug exposure, that TD may be a motoric component of a more severe, pan-neurological form of schizophrenia. Because of the severity of symptoms in this form of the condition, patients would routinely receive higher doses of antipsychotic therapies, thus generating the idea of a causal relationship between medication and TD. One unambiguous contribution of the SGAs, which produce lower rates of TD, is that—whether or not some medications may cause TD—exposure to these agents exacerbates what may be a preexisting condition. Those CATIE individuals who did not have evidence of TD had been treated with antipsychotics for >14 years. It is possible that they represent a different subgroup, with a reduced risk for both EPS and TD.

Substance Abuse

Substance abuse comorbidity is associated with adverse outcomes for patients with schizophrenia.[10] Poor compliance, relapse, violence, and criminal behavior are more frequent among such patients compared to nonusers.[10] Self-report about substance use is notoriously unreliable, however, and urine testing has a window of detection of less than 24 hours. During the CATIE trial, a variety of detection methods were used to estimate substance use and abuse—including multiple informant reports from patients, families, and clinicians, as well as urine drug testing. A novel measure used in CATIE was based on radioimmunoassay of hair follicles.[2,3,24] Hair analysis relies on the observation that drugs and their metabolites are transferred from the capillary circulation to the hair follicle, thus providing an enduring record of their use. As hair grows, the drugs accumulate in the hair shaft, a natural storage depot, and can be analyzed in segments. The rate of hair growth allows one to estimate corresponding time periods of substance use. Hair grows approximately one half inch per month; therefore, the half inch of hair nearest the scalp reflects usage over the previous 30 days. This method reliably detects drugs of abuse including marijuana, opiates, cocaine, phencyclidine, and amphetamines.

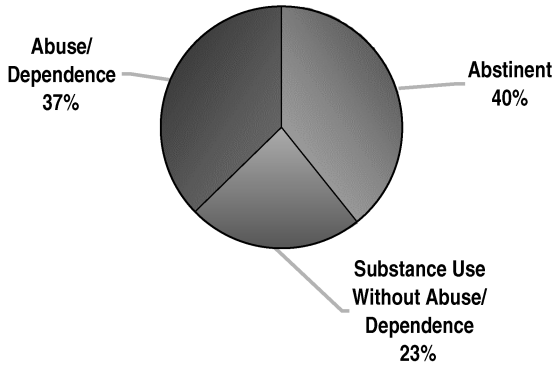

FIGURE 5. Substance use in CATIE subjects (alcohol and illicit drugs). Source: Swartz et al. (2006).[10]

Among CATIE subjects, abuse of, or dependence upon, alcohol or illicit drugs was detected in 37% of the patients. Substance use without abuse or dependence was found in 23% (see Figure 5). Forty percent of the sample was abstinent. Substance abuse and dependence correlated strongly with a history of childhood conduct disorder. Ironically, patients who used or abused alcohol or marijuana tended to function as well as nonusers. Substance use disorders were not associated with negative symptoms or deficit features. Cocaine involvement substantially disrupted the psychosocial functioning of patients with schizophrenia.[10,24] Polysubstance abuse was common in this sample. Of the total sample, 52% drank alcohol, 23% used marijuana, and 19% used cocaine. Among the abuse/dependence subsample, 87% drank alcohol, 44% used marijuana, and 36% used cocaine.

Violence

Elevated rates of violence in schizophrenia are associated with comorbid substance abuse.[10] Despite the low prevalence of violence among schizophrenic individuals, its presence creates obstacles to treatment, higher cost of care, stigma, community exclusion, and so on, which underline the need for better understanding.[25] The CATIE study examined serious violence and minor violence, as well as a combined measure of any violence. Serious violence was defined as any assault using a lethal weapon or resulting in injury, any threat with a lethal weapon in hand, and any sexual assault. "Other aggressive acts, or minor violence," included simple assault without injury or weapon use (for instance pushing, shoving, or slapping). Six-month prevalence of violent behavior by self-report and collateral report was obtained at baseline. These data indicated that minor violence was present in 15.5% of the sample ($n = 219$), and serious violence was present in 3.63% of the sample

($n = 51$), for a combined total of 19.15% of the sample ($n = 270$). Overall, these data confirm that medicated individuals with schizophrenia have a relatively low rate of violent behavior.[26]

For minor violent behavior, risk factors included both demographic factors (e.g., younger age, female gender, unemployment), household composition (e.g., more family members, not feeling supported/listened to, and limited social contact), and housing (e.g., restrictive living situation, as in a group home). For serious violence, childhood risk factors (e.g., two or more features of childhood antisocial disorder) and younger age were predictors.[25]

Clinical and functional correlates of violence in the CATIE sample were reflected in other data: PANSS negative symptom scores were negatively associated with serious violence, whereas positive symptom scores above the median were associated with serious violence.

The overall results indicated that violence in this sample is associated with multiple factors, including the presence of psychotic symptoms (positive symptoms), history of childhood conduct problems, living with family members, and victimization. These factors accounted, however, for a relatively low proportion of the variance in the study. The findings are consistent with clinical intuition that positive psychotic symptoms such as persecutory ideation would increase the risk of both minor and serious violence. Furthermore, negative symptoms, such as social withdrawal, lower the risk of serious violence. Clusters of symptoms may increase or decrease violence risk in patients with schizophrenia. Clinicians providing community-based treatment should be aware of the clinical and nonclinical risk factors that increase the potential for violence.[25,26] Serious violence was associated with psychotic and depressive symptoms, childhood conduct problems, and victimization.

Cost-Effectiveness

The cost of antipsychotic drugs in the United States is estimated to be greater than $10.5 billion in 2005, a figure that has grown steadily and is largely (roughly 90%) due to SGAs. This staggering amount has spurred efforts to determine the cost-effectiveness of SGAs.[27] Under such an analysis, if a program costs more than the value of its benefits, it is not rational to implement or maintain it. Further, if health gains are similar with different strategies, it is rational to use cost as the basis for choosing between the available strategies.[27,28] The CATIE trial comprehensively identified the sources of costs associated with antipsychotic drugs: the cost of the medications themselves, of inpatient, outpatient, and emergency visits, and so on. Average total health care costs were 20–30% lower for perphenazine than for the SGAs, due almost entirely to the higher drug costs for the latter. The cost differences were in a range of $300 to $500 per month. Are these costs justified by the benefits in terms of quality of life or avoidance of risks such as TD? To measure effectiveness, different approaches were employed: (1) PANSS total score for symptom comparisons between groups; (2) a standard cost-effectiveness outcome measure, namely, the health state utility in quality-adjusted life years (a measure consistent with Centers for Disease Control recommendations for a single standard estimate); (3) a visual-analogue scale to capture a subjective patient global rating of overall health; and (4) an item from the Lehman Quality of Life questionnaire rating life overall from terrible to delightful. The results from each approach were similar: there were no significant differences in any of the four measures among the antipsychotic agents in the study.

There are certain limitations in this analysis of cost-effectiveness. For example, the study sample was not representative of all subgroups of schizophrenia: elderly patients, treatment-resistant patients, early-onset or first-episode patients, and patients satisfied with their medication therapy were excluded. Furthermore, the study's duration may have been too short to detect differences in TD or cardiovascular illness that may eventually affect quality-of-life assessments. Failure to detect differences is not the same as no differences; the measures may be inadequate.

In spite of these caveats, the findings in this aspect of the study are striking (and similar to other studies)[29] and invite a reassessment of current clinical economics in the treatment of schizophrenia. The findings do provide, however, a snapshot of the current situation. Other limitations include the potential impact of changing drug prices (e.g., through already scheduled replacement of branded drugs with generic formulations) and the possibility of different outcomes with future antipsychotic compounds. The primary cost-effectiveness outcome measure, health state utility in quality-adjusted life years, has the inherent methodologic weakness of being a reflection of social (and subjective) preferences for various health states. Specifically, these preferences are ones derived from various individuals and groups in response to requests to estimate the impact of specific psychiatric-symptom experiences, not the preferences of patients themselves.

CONCLUSIONS

The most striking finding from CATIE was that most patients discontinued antipsychotic therapy with a frequency that gives olanzapine only a slight effectiveness advantage—least likely to be discontinued (36% of olanzapine subjects completed the trial on the medication to which they were initially randomized vs. 18% to 28% for the other medications). A second striking observation was that perphenazine was as effective as three of the other atypical

agents and was as well tolerated as several of the newer agents. Clozapine remained the most effective drug for patients who did not respond to their first antipsychotic treatment. For those taking a second SGA because of tolerability concerns, olanzapine and risperidone were more effective than quetiapine and ziprasidone. Metabolic effects varied among the agents, with weight gain being particularly associated with olanzapine, and reduction in lipids and glycosylated hemoglobin levels associated with ziprasidone.

DISCUSSION

The CATIE trial is among the most expensive research projects ever funded by NIMH. The high rate of discontinuation of all SGAs was not initially anticipated but is consistent with data from other long-term trials. An equally unforeseen outcome was that perphenazine demonstrated similar effectiveness to the SGAs, raising important questions about how we evaluate the impact of our treatments and relate cost to their specific benefit. Phase 2 data suggested that clozapine should be considered after adequate trials of two SGAs had been completed. While there are limitations in this study, these findings should stimulate useful discussion.

The CATIE trial provided important information on other dimensions of schizophrenia, particularly on the health and experience of a large sample of affected patients[30–32] These observations have substantial public health significance, illuminating substance abuse patterns, violence, and co-occurrence of metabolic disorder, TD, and impaired cognition. The CATIE trial was not designed as an epidemiologic study, but its sample size and the geographical distribution of study sites substantiate its value as an important estimate of national experience in these areas.

The long-term impact of CATIE will be evaluated in terms of the groundbreaking nature of its design innovations,[4,7,33] its scale, its precedent-setting involvement of NIMH in field studies of treatment, and, finally, from the specific findings of the CATIE trial itself. This federal investment, largely free from the potential bias of industry support, adds a positive dimension to therapeutic research. The decision to maintain support for a subset of CATIE research sites (now referred to as the Schizophrenia Trial Network) to facilitate collaboration on high-priority public health issues in schizophrenia treatment—such as first-episode interventions, polypharmacy, treatment adherence, treatment resistance, metabolic disorder, and medical comorbidity—may move the field of therapeutics along in a swifter and more rigorous manner.

Many questions about the study design have been raised. Among the more cogent concerns are the following:

- *Dosing*. Fewer than half of CATIE subjects received the maximal drug doses permitted in the study protocol. Only 40% of the maximal level dose of olanzapine, risperidone, or perphenazine, 44% of the maximal level dose of quetiapine, and 48% of the maximal level dose of ziprasidone were actually used. Mean modal medication doses were 20 mg for olanzapine, 543.4 mg for quetiapine, 3.9 mg for risperidone, 20.8 mg for perphenazine, and 112.8 mg for ziprasidone. These doses are somewhat representative of typical outpatient treatment doses for risperidone and perhaps olanzapine, but not necessarily for quetiapine, perphenazine, and ziprasidone. In our experience, for example, many patients require (and tolerate) higher doses of risperidone and ziprasidone. Some observers have asserted that the SGAs would have separated from perphenazine in effectiveness, or at least performed somewhat better, if more aggressive dosing had been employed. And some have argued that the slight advantage of olanzapine may be attributed to its higher dosing in the trial, including its relatively higher starting dosage.
- *Bias*. One of the goals of CATIE was to achieve a design free of industry bias. Except for the dose range issue noted above, this goal may have been achieved. However, bias can arise in many forms. One such bias may have been to afford patients in the study more of a role in drug selection. Patients were well aware of the multiple drug alternatives available in the trial. And while difficult to ascertain, the suggestion that this feature encouraged discontinuation regardless of treatment impact is a distinct possibility. To reach consensus among the responsible interested parties and research scientists—which was required in order to proceed with the CATIE trial in the first place—it may have been difficult to decide upon certain design strategies (such as fixed or higher doses for each medication) that may have been more likely to separate out the studied agents.
- *Prior medication*. Among subjects, 22% were taking olanzapine prior to enrolling in CATIE; 23% of these subjects were then randomized to continue olanzapine.[4,34] Similar numbers obtained for risperidone. For individuals randomized to olanzapine and risperidone who were continuing their baseline medication, the time until discontinuation was significantly longer than for those assigned to switch to another antipsychotic from the one they had been receiving. These observations merit further investigation, although Essock and colleagues[34] report that the main findings of CATIE were unchanged when controlling for prior exposure.
- *All-cause discontinuation as primary outcome measure*. The rationale for this measure was understandable and corresponds well to the tenets of effectiveness trials. But in the real world of the CATIE trial,

subjects were highly aware of the alternative drug choices available under the trial's design. This factor may have influenced patient decisions to switch (i.e., discontinue) their current medications. Together with the controversial dose range for olanzapine (which exceeded the package insert guidelines), this feature may have influenced the outcome of the study.

A number of additional issues have been raised by the initial CATIE design. Is individual variation in treatment response predictable, or (at least) do pretreatment factors inform the selection of medication? Differences in tolerability and efficacy occur at an individual level rather than at a group level. Therefore, do averaged findings provide meaningful guidance to clinicians treating a particular patient? We amplify this point below.

- *Perphenazine as a representative FGA*. Perphenazine was selected as the comparator FGA because it falls between haloperidol (most EPS effects, fewest muscarinic side effects; the so-called high-potency FGA) and chlorpromazine (fewest EPS effects, greatest muscarinic effects; the so-called low-potency FGA). Although perphenazine was introduced in the 1960s, thus making it an FGA, its first metabolite—n-dealkylperphenazine—has reduced dopamine receptor D2 subtype affinity and greater serotonin (5-HT2A) affinity. This pattern of pharmacological properties may make perphenazine behave more like an SGA than an FGA such as haloperidol or chlorpromazine.
- *The problem of matching drug and patient in a heterogeneous disorder*. The principal objective of CATIE was to compare SGAs to each other and to perphenazine, a midpotency FGA. Physicians treating large numbers of schizophrenic patients with SGAs may have been surprised to learn that the differences among them were small, but presumably few were surprised to learn that no one drug is appropriate for all patients. Experienced practitioners recognize that they must find the right agent to fit each patient's unique pattern of response as well as his/her array of side effects. That raises the question whether the CATIE findings help improve our ability to match drug treatment to patient. Those findings confirm the continuing problem of optimally fitting drug to patient. But the data collected in the study may potentially be useful for addressing that issue (see immediately below).

Many of the CATIE subjects donated blood for future genetic studies. Analysis of these samples may shed light on why schizophrenic patients who exhibit similar symptomatology respond differently to the same drug. More than 25 candidate genes for schizophrenia have been identified—which is consistent with the observed heterogeneity of the disorder's clinical psychopathology. One could imagine a polygenic model in which different numbers and combinations of these or possibly even other candidate genes produce an array of phenotypes with differing degrees of severity and varied responses to specific antipsychotic agents. By analyzing the DNA samples of those subjects who respond differentially, we may be able to identify markers that correlate with drug response and also enhance our understanding of this complex condition. Such pharmacogenetic approaches may eventually result in highly individualized treatments.

Analysis of the data in studies like CATIE assumes homogeneity of the population being sampled (in this case, schizophrenia). By the same token, schizophrenia is taken to be a unitary disease—rather than the alternative formulation that it is a syndrome. We prefer the latter position that schizophrenia is the result of different genetic and environmental factors that produce an overlapping phenotype. This conclusion, at its extreme, suggests that the 1460 CATIE subjects may represent as many as 1460 different phenocopies. At a less extreme level, the possibility of examining response according to subtypes such as family history, paternal age, or presence of the deficit syndrome might be fruitful.[35,36]

With this perspective, an alternative approach to the current analysis of CATIE might be a bottom-up rather than a top-down approach. Starting with the subject's DNA, one could look for correlation between specific candidate genes and specific phenotypic expressions of schizophrenia's clinical presentation (including, for example, first-rank symptoms, the deficit syndrome, cognitive impairment, neurological signs and symptoms, neuroanatomical abnormalities), as well as treatment response (including side-effect tolerance [e.g., the observation that some patients on either clozapine or olanzapine develop no manifestations of MS, while the majority of patients receiving these agents have either a significant or a severe problem]). This more individualized strategy could yield reproducible data that might ultimately lead to an informed basis for treatment selection based on the biological substrate of the condition rather than on its clinical manifestations.

Another consideration is inspired by the adage that therapeutic success generally precedes understanding of clinical disease: using the single-patient approach, could subjects in CATIE who had especially successful outcomes be a source of genotypic information informing new hypotheses to predict their responses?

CLINICAL IMPLICATIONS

For reasons of both safety and efficacy, the clinical trial is the primary method for evaluating pharmacological agents in every area of medicine, including psychiatry. But in most

Principles of Antipsychotic Treatment in Schizophrenia

- Schizophrenia is a lifelong disorder.
- Medication maintenance is essential to prevent relapses, which interfere with recovery.
- Therefore, medication adherence is a fundamental treatment goal and is associated with better clinical outcomes.
- The major cause of relapse is nonadherence.
- Tolerability of antipsychotics makes compliance more likely and relapses less likely.
- No antipsychotic is effective in all cases.
- Given generally comparable efficacies of CATIE antipsychotics, *safety* and *tolerability* should be significant factors in medication selection.
- Achieving maximal effectiveness calls for
  - a sound therapeutic alliance
  - an ongoing process of informed consent
  - clinical education of patient and, if appropriate, family members and others
  - ongoing education about the illness and general health issues
  - careful dosing
  - systematic assessment of psychopathology responses
  - monitoring metabolic risks
  - avoiding EPS (and anticholinergic effects)
  - minimizing impact of other side effects.
- Clinical psychiatric treatment requires vigilance to assure and maintain psychiatric and medical health.

areas of medicine, outcomes can be objectively quantified and are often unitary in nature. Changes in blood pressure, reduction in tumor mass, and control of blood sugar or cholesterol levels are all single, measurable outcomes. In psychiatry, we measure complex behaviors, some with no or limited measurable characteristics (such as delusions). While the standard design of the clinical trial has been invaluable in the development of improved medications, CATIE was undertaken specifically because so many questions had been raised as to whether the SGAs were actually better than FGAs and whether some SGAs were better than others. At this point we have some useful information on this question, but still other questions remain unanswered.

Among its many observations, CATIE has confirmed that psychiatric symptomatology does not predict patients' responses to specific agents in terms of either efficacy or tolerability. Our interpretation of this finding is that any encounter between a prescribing mental health provider and patient is best understood as an individual clinical trial informed by the broadest generalities of clinical experience, the patient's previous responses to antipsychotic medication, a healthy skepticism of marketing claims, and, finally, critical review of recent findings in the literature. Guidance comes from the best data available, key clinical principles (see text box), and the art of clinical decision making.

We wish to conclude with a caveat. The CATIE design intended to sample a "real world" study population in terms of patient recruitment, treatment regimens, and treatment settings. But the "real world" of CATIE is not the real world of clinical practice. Because of the several excluded populations, the choice of perphenazine as the comparator FGA, and the duration of the study (not the many years of chronic disease), it is imperative that readers recognize that results from CATIE have not conclusively established that SGAs are no better than FGAs. What CATIE has demonstrated is that the more rigorously one examines complex clinical data designed to be pooled and analyzed, the more complicated/ambiguous each specific issue can become. Current clinical practice and future clinical studies must be refined in light of these newly appreciated complexities. Psychiatric research attempts to deconstruct disorders of the brain for the purpose of illuminating that endlessly complex structure. It is no small task.

SUMMARY

There are problems with the CATIE trial and controversial features to be sure. Criticism of the dosing regimen, the design decisions concerning participants with TD, aspects of the perphenazine component of the trial, and the strategies for evaluating cost-effectiveness are among them. But such criticisms are to be expected; no study is without limitations. The observations reported in the CATIE trial are valuable starting points for sharpening debate and focusing efforts to do better in the future.

The CATIE trial has been a monumental undertaking that has generated salient observations and considerable controversy. Despite its impressive accomplishments—especially its pragmatic focus and its effort to eliminate biases that have undermined confidence in previous SGA drug trials—it does not answer all the questions that it was designed to address. Indeed, research seldom provides comprehensive answers to guide clinical decision making. Research requires replication, extension of findings to new samples, and refined interpretation. The clinician is left ultimately to take this and other relevant information, and to translate it into practical applications for particular patients.

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