# The Roles of Efficacy, Safety, and Tolerability in Antipsychotic Effectiveness: Practical Implications of the CATIE Schizophrenia Trial



Henry A. Nasrallah, M.D.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) series of studies has set a standard for trials in schizophrenia. Included in the 3-phase National Institute of Mental Health–sponsored series were 1460 patients drawn from 57 sites in 24 states. This was designed as a "real-world" practical clinical trial, including a broad array of patients and asking straightforward, clinically relevant questions. The primary aim was to compare the available atypical agents olanzapine, quetiapine, risperidone, and ziprasidone—to each other and to the typical agent perphenazine—with regard to drug effectiveness and tolerability. In general, the various agents studied were similar, with olanzapine being relatively the most effective, as measured by treatment discontinuation. This might be due in part to the more optimal dosing of olanzapine compared with the other antipsychotics. In the study arm that included clozapine, that agent was shown to be more effective than olanzapine, quetiapine, or risperidone. Perphenazine tended to perform as well as the atypical agents. Except for clozapine, olanzapine clearly had the greatest metabolic side effect burden, and ziprasidone, the least. Perphenazine had the most motor side effects, although the rate was modest.

*(J Clin Psychiatry 2007;68[suppl 1]:5–11)*

Publication of the primary findings of the long-awaited Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial[1] has set the stage for dissemination of a large body of data on the comparative effectiveness of old and new antipsychotics in schizophrenia. A massive sample—1460 subjects with chronic schizophrenia—were administered up to 3 of 8 antipsychotics in 2 blinded phases and a third open-label phase. Funded by a grant of more than $50,000,000 from the National Institute of Mental Health (NIMH), the CATIE trial was conducted in 24 states at 57 geographically, demographically, and organizationally diverse sites. The initial report had an immediate impact and generated much controversy, which is expected to continue as additional findings unfold in the years to come. Although many questions remain to be answered, the articles in this supplement address some of the many facets of CATIE and attempt to unravel the complexities of this extraordinary study.

*From the Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio.*

*This article is derived from the planning teleconference "Evaluating the Evidence: Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Beyond," which was held on May 10, 2006, and was independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and Health and Wellness Education Partners (HWeP) pursuant to an educational grant from Pfizer Inc and additional financial support from HWP Publishing.*

*Dr. Nasrallah is a consultant for, has received honoraria from, and been on the speakers/advisory boards for Abbott, AstraZeneca, Janssen, Pfizer, and Shire and has received grant/research support from AstraZeneca, Janssen, and Pfizer.*

*Content development and writing support for this article was provided in part by an independent writer contracted by HWeP: Martin Korn, M.D., a psychiatrist in private practice in New York.*

*Corresponding author and reprints: Henry A. Nasrallah, M.D., Department of Psychiatry, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0559 (e-mail: henry.nasrallah@uc.edu).*

## EVOLUTION OF ANTIPSYCHOTICS

The introduction in 1954 of the first antipsychotic, chlorpromazine, was a milestone in the pharmacologic treatment of chronic schizophrenia. Few somatic treatments were available prior to this time, and those that were available were extremely limited in their effectiveness. Chlorpromazine was able to alleviate a broad range of severe symptoms including delusions, hallucinations, aggression, anxiety, and disordered thinking. Yet, it was clear from the beginning that this medication, exceptional as it was for its time, produced only partial symptomatic relief.[2]

In the ensuing decades, many other antipsychotics similar to chlorpromazine were introduced. Among these were the low-potency agent thioridazine, the mid-potency agents trifluoperazine and perphenazine, and the high-potency agents haloperidol and fluphenazine. These "first-generation" or "typical" antipsychotics shared a common element in that all were potent dopamine-2 ($D_2$) receptor antagonists. Blockade at the various central nervous system dopaminergic pathways resulted in both the positive actions of the drugs and their unwanted side effects. Do-

  

pamine receptor blockade at the mesolimbic pathway was thought to ameliorate psychosis and accounted for many of the positive effects of the drug. However, excessive dopamine receptor blockade in the mesocortical pathway might worsen negative symptoms and cognition in an already impaired individual. Blockade at the tuberoinfundibular system could lead to unwanted prolactin elevation, and with long-term use, dopaminergic antagonism in the nigrostriatal system might produce acute and chronic extrapyramidal symptoms, including tardive dyskinesia (TD).[3]

Clozapine was the next landmark in the treatment of schizophrenia. Originally synthesized in 1959, it was initially observed not to exert any extrapyramidal side effects—a characteristic at the time considered a sine qua non of antipsychotic efficacy—nor did it elevate prolactin. It was later found to be very effective and was approved in Europe in 1972, only to be temporarily withdrawn by the manufacturer in 1975, when fatalities occurred due to agranulocytosis.[4] In 1988, Kane and colleagues[5] demonstrated that clozapine was more effective in treating patients with refractory schizophrenia compared with chlorpromazine. Clozapine was labeled an "atypical" agent due to its complete lack of the extrapyramidal side effects that were associated with every agent in the first generation of neuroleptics. Clozapine lacked the tight $D_2$ receptor binding capacity of earlier agents,[6] but was found to bind to numerous other receptors, which might help to explain its unique therapeutic mode of action. Yet, because the clinical advantages of clozapine were offset by a plethora of side effects, including agranulocytosis, a search began for other atypical agents that were as clinically effective as clozapine with a more benign side effect profile. Risperidone was the next atypical agent, soon followed by olanzapine, quetiapine, ziprasidone, and aripiprazole. Each of these atypicals also had distinct receptor profiles that offered the promise of differential efficacy with varying side effect and clinical profiles.[7]

## RATIONALE BEHIND CATIE

As the number of choices evolved, the question of differential effectiveness became more pressing. Was one atypical better or safer than another? Were any or all of the second-generation (atypical) agents better than the first-generation (typical) agents? Were the atypical agents more helpful in alleviating negative physical or cognitive symptoms? Numerous clinical trials—predominantly sponsored by industry—were conducted in an effort to answer these questions. The results, however, have often been confusing and inconsistent.[8]

In a recent report, Heres and colleagues[8] analyzed 42 head-to-head studies of atypical antipsychotics and found that there arguably was a bias in industry-sponsored studies. In 90% of studies supported by pharmaceutical companies, the outcome favored the sponsoring company. The possible sources of bias included doses administered, rate of dose escalation, entry criteria, population studied, statistical methods, reporting of results, and wording of findings. Further, most of the studies were short, lasting only 6 to 12 weeks. These discrepancies limit the validity of the studies.

The need to answer these basic questions became all the more pressing as the expenditure for atypical agents continued to expand. It is with this backdrop and in an effort to better address clinical and cost-effectiveness issues that the NIMH sponsored the CATIE trials as part of its series of large multicenter best-practices initiatives. Others include the Treatment for Adolescents with Depression Study (TADS),[9] the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[10] the Sequenced Treatment Alternatives to Relieve Depression (STAR*D),[11] and the CATIE trial for Alzheimer's disease.[12] These extended pragmatic trials have been termed "practical trials" or "effectiveness trials," as differentiated from the traditional short-term "efficacy trials" customarily utilized in U.S. Food and Drug Administration registration trials.[13]

March and colleagues[14] assessed and outlined 8 requirements that a practical clinical trial in psychiatry—such as CATIE—needs to satisfy if it is to maximize the impact on clinical decision making. The criteria are as follows:

- Questions posed should be straightforward and clinically relevant.
- Trials should be carried out in settings that are representative of real-world clinical practices to ensure results can be generalized.
- The study should be sufficiently powered to detect small to moderate clinically relevant outcomes. Practical trials tend to be larger than efficacy trials, and thousands rather than hundreds of patients may be required.
- Randomization should be used, to protect against bias and confounding variables.
- There should be clinical uncertainty about the outcome of treatment.
- Outcomes should be simple as well as clinically meaningful. Unambiguous and readily detectable endpoints help to simplify data collection.
- Assessments and treatments should reflect best clinical practices.
- Subject and investigator burden should be minimized.

Efficacy trials, in contrast to practical trials, tend to be narrowly focused, have more restrictive inclusion criteria, and usually compare one drug against another drug and/or placebo. The primary outcome measures and focus of attention in efficacy trials are research rating scales. Effectiveness trials include a broad spectrum of patients, com-

  

Table 1. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study Design[a]

| Phase[b] | Drugs Studied |
|---|---|
| Phase 1—1460 patients with schizophrenia randomly assigned to double-blind treatment[c] | Olanzapine<br>Quetiapine<br>Risperidone<br>Ziprasidone<br>Perphenazine |
| Phase 2—Participants who discontinue phase 1 choose either the clozapine or the ziprasidone randomization pathway and are randomly assigned to a treatment they did not previously receive in this study | 50:50 random assignment to ziprasidone vs another atypical antipsychotic (olanzapine, quetiapine, or risperidone)<br>50:50 random assignment to clozapine vs an atypical antipsychotic (olanzapine, quetiapine, or risperidone) |
| Phase 3—Participants who discontinue phase 2 choose an open-label treatment | Aripiprazole<br>Clozapine<br>Fluphenazine decanoate<br>Olanzapine<br>Perphenazine<br>Quetiapine<br>Risperidone<br>Ziprasidone<br>2 of the antipsychotics on this list |

[a]Based on Stroup et al.[16,17]
[b]Patients who do well on a treatment remain on it for 18 months.
[c]Patients who fail perphenazine are randomly assigned to an atypical before phase 2.

Table 2. Differences Between CATIE and Most Controlled Efficacy Trials

| Study Characteristic | CATIE[a] | Most Efficacy Studies |
|---|---|---|
| Size | 1460 patients | Numbers in the 100s |
| Diversity of sites | 5 types of settings | 1 to 2 setting types, often academic |
| Length of study | 18 mo | Often less than 3 mo |
| Substance abuse | Allowed | Usually excluded |
| Medical problems | Allowed if not acute or unstable | Usually excluded |
| Medical adjunctive medications | Allowed | Usually limited |
| Psychotropic adjunctive medications | Allowed except for antipsychotics | Limited |
| No. of drugs studied | 6 drugs in phases 1 and 2; 2 more in phase 3 | 1 to 2 drugs and/or placebo |
| Placebo | Not included | Frequently included |
| Funding | Entirely NIMH funded | Pharmaceutical and/or independent grant funding |
| Comparison drug | Medium-potency perphenazine at lower doses | Frequently haloperidol, often used in higher doses |
| Switching to other drugs | Allowed | Rarely an option |

[a]Based on Lieberman et al.[1]
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, NIMH = National Institute of Mental Health.

pare active treatments against each other, and focus on practical, real-world outcome measures. Traditional research studies are narrowly focused, and the outcome may not have specific relevance to the clinician. For example, research trials in depression usually focus on major depression rather than the less severe subsyndromal forms that may be more commonly encountered in clinical practice.[15]

## OVERVIEW OF THE CATIE TRIALS

The CATIE trials combined features of both efficacy trials and practical clinical trials.[16] Very straightforward and clinically relevant questions were posed: Were the atypical agents more effective than typical agents? Which medications had the most serious or benign side effect profiles? Was clozapine more effective than the other atypicals in patients who did not respond adequately to another antipsychotic?

There were 3 phases in the CATIE trials, as shown in Table 1.[16,17] With 1460 patients included in phase 1, CATIE is far larger than most published clinical trials, in which 200 to 300 participants comprise a reasonably sized study (Table 2).[1] The number of drugs tested was also impressive, as 6 drugs were included in phases 1 and 2, and 8 in the open-label phase 3. In comparison, most studies compare just 1 drug to another drug and/or placebo. CATIE patients were followed over an 18-month time span, while most drug studies in schizophrenia are usually conducted over a much shorter period of time (e.g., 2 to 3 months).

CATIE was successful in reflecting a real-world clinical population, as demonstrated by its diverse range of sites. Patients were drawn from 57 sites in 24 states, including 16 university clinics, 10 state mental health agencies, 7 Veterans Affairs medical centers, 6 private nonprofit agencies, 4 private-practice sites, and 14 mixed-system sites. Most efficacy studies draw from 1 or 2 types

  

of sites, often in large part from academic centers. Patients actively using drugs or alcohol were allowed in CATIE; 37% were diagnosed with either substance abuse or dependence and 22% were using drugs or alcohol but did not meet criteria for abuse or dependence.[18] These findings reflect the high rate of substance abuse in patients with schizophrenia.[19] Patients with nonserious or stable medical conditions were also allowed in the study. Adjunctive prescription medications were permitted as long as they were not antipsychotics. Excluded from CATIE were patients having had only 1 schizophrenic episode, individuals with a diagnosis of schizoaffective disorder, and those with documented treatment resistance. The drugs were all of the available atypical agents including clozapine, olanzapine, risperidone, and ziprasidone, as well as the typical agent perphenazine. Clozapine was not included until phase 2 of the study, when the issue of treatment failure was examined. In the open-label phase 3, fluphenazine decanoate was added along with aripiprazole. In addition, a combination of 2 antipsychotics was allowed for patients who dropped out from both phases 1 and 2.

One of the most significant decisions of the study was the selection of the primary outcome measure, which was "time to discontinuation" for any cause. This measure was considered to be a reflection of 4 different treatment discontinuation endpoints: lack of tolerability (initiated by the patient), lack of efficacy (initiated by the physician), clinician decision (e.g., safety concerns such as abnormal laboratory values), and patient decision (electing to terminate for any reason).

The all-cause discontinuation measure is a proxy for the decision process in the real world, that being an ongoing joint evaluation by clinician and patient as to whether a particular treatment is acceptable or needs to be changed. Secondary outcome measures included the specific reasons for discontinuation, as well as scores on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions scale. Change in cognitive function was also measured. Safety outcomes were evaluated at months 1, 3, 6, 9, 12, 15, and 18, including measures of neurologic side effects, weight changes, electrocardiogram findings, and laboratory findings.

## Phase 1 Trial

In phase 1 of the study, the atypical agents olanzapine, quetiapine, risperidone, and ziprasidone were compared to the typical agent perphenazine as well as to each other.[1] Since ziprasidone was not available for clinical use at the start of CATIE, this drug was not included until approximately 40% of the patients had been randomly assigned to the other drugs. Statistical comparisons to ziprasidone were made only to patients who entered the study after this drug was included. Aripiprazole was not included because it was not approved for use until the recruitment period had ended.

Table 3. Dose Ranges and Averages in CATIE Trial and Common Doses[a]

| Medication | Dose Range, mg/d | Average Dose, mg/d | Average Dose in Community (standard maximum), mg/d |
|---|---|---|---|
| Olanzapine | 7.5–30 | 20.1 | 14 (20) |
| Perphenazine | 8–32 | 20.8 | 16 (64) |
| Quetiapine | 200–800 | 543.4 | 388 (800) |
| Risperidone | 1.5–6 | 3.9 | 3.8 (16) |
| Ziprasidone | 40–160 | 112.8 | 125 (200) |

[a]Data from Lieberman et al.,[1] Nasrallah,[20] MedLine Plus,[21] and, on community doses, from Jibson et al.[22]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

There were 1460 patients included in phase 1. For ethical reasons and to avoid possible exacerbation, 231 patients who manifested evidence of TD at entry into the study were randomly assigned only to second-generation agents rather than to perphenazine. To prevent possible bias due to their additional neurologic and psychiatric challenges, TD patients were excluded from the statistical analyses among antipsychotics.

Patients were administered up to 4 capsules of drugs, all identical in appearance; the dosages are shown in Table 3[1,20,21] along with dosages generally used in the community.[22] However, the average community dose of antipsychotics in patients with chronic schizophrenia, such as those in the CATIE sample (average duration of illness of 15 years), may not necessarily be a valid optimal dose for such patients, and higher doses are often found to be needed.

There were differences in the number of patients taking the various drugs prior to entry into the study. Most (22%) were taking olanzapine, followed by risperidone (19%) and quetiapine (7%). Seven percent were on treatment with a combination of atypical agents, and 16% were on treatment with typical antipsychotics.[1] Because ziprasidone was not marketed until the midst of the study, no patients were receiving this medication at entry.

The most prominent finding of the CATIE trial is the high (74%) all-cause discontinuation rate for all drugs (see Table 4 for comparisons).[1] That is, at the 18-month completion point, 74% of all subjects were not taking the agent they started with. The time to discontinuation for olanzapine-treated patients was significantly longer than for risperidone ($p = .001$) and quetiapine ($p = .002$). The differences between olanzapine and either perphenazine or ziprasidone were no longer significant after adjusting for multiple comparisons, possibly due to lower sample sizes for the latter 2 agents.[1]

Although olanzapine was associated with a longer duration of treatment than the other antipsychotic drugs as measured by all-cause discontinuation rates, it was also associated with the highest frequency of metabolic side effects including increases in weight, blood glucose,

  

Table 4. Percentage of CATIE Patients Who Discontinued Medication[a]

| Medication | Overall Discontinuation Rate at 18 Mo | Efficacy Discontinuation Rate | Tolerability Discontinuation Rate |
|---|---|---|---|
| Olanzapine | 64 | 15 | 19 |
| Perphenazine | 75 | 25 | 16 |
| Quetiapine | 82 | 28 | 15 |
| Risperidone | 74 | 27 | 10 |
| Ziprasidone | 79 | 24 | 15 |

[a]Data from Lieberman et al.[1]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

glycosylated hemoglobin, cholesterol, and triglycerides (Table 5),[1,23] which is consistent with the pre-CATIE literature.[24] In contrast, patients treated with ziprasidone had the best overall metabolic profile. There were no statistically significant differences between the rates of extrapyramidal side effects, movement disorders, or akathisia. However, more patients (8%) discontinued the older antipsychotic perphenazine due to motor side effects compared with those taking the atypical antipsychotics (2% to 4%).[1]

### Phase 2 Trial

Phase 2 consisted of 2 pathways.[17] Patients who discontinued phase 1 prior to 18 months due to lack of efficacy could be randomized to what was called an efficacy or clozapine arm of phase 2.[25] The other pathway of phase 2 was termed a tolerability or ziprasidone arm.[17] Subjects in this arm were those who terminated phase 1 due to tolerability issues and those who had lack of efficacy in phase 1 but refused to receive clozapine.

The clozapine (efficacy) arm consisted of 99 total patients.[25] Subjects were assigned to receive either open-label clozapine (N = 49) or double-blind treatment with olanzapine (N = 19), quetiapine (N = 15), or risperidone (N = 16). Since clozapine required weekly blood drawing to monitor for agranulocytosis, the investigators made a decision to administer clozapine in open-label fashion. The time until treatment discontinuation for any cause was significantly longer for clozapine (10.5 months) compared with quetiapine (3.3 months), risperidone (2.8 months), and olanzapine (2.7 months). The overall all-cause discontinuation rate was 69%. At the 3-month assessment period, the PANSS total score had decreased significantly more for patients receiving clozapine compared with those for patients receiving quetiapine and risperidone, but not olanzapine. There were no significant differences in side effect profiles, in part due to the small number of subjects.[25]

The ziprasidone (tolerability) pathway consisted of 444 patients.[17] Included in the analysis were the patients randomly assigned to the 4 treatments: olanzapine (N = 66), quetiapine (N = 63), risperidone (N = 69), or ziprasidone (N = 135). The median time to treatment discontinuation

Table 5. Metabolic Effects of Drugs Among Patients in CATIE Phase 1[a]

| | | | | | |
|---|---|---|---|---|---|
| Weight change for the duration of treatment in phase 1, mean, lb | P −2.0 | Z −1.6 | R 0.8 | Q 1.1 | O 9.4 |
| Proportion of patients gaining > 7% body weight, % | Z 7 | P 12 | R 14 | Q 16 | O 30 |
| Average weight change per mo, lb | Z −0.3 | P 0.2 | R 0.4 | Q 0.5 | O 2.0 |
| Blood glucose increase, mean, mg/dL | Z 2.3 | P 5.2 | R 6.7 | Q 6.8 | O 15.0 |
| Hemoglobin $A_{1c}$ change, mean, % | Q 0.05 | R 0.08 | P 0.1 | Z −0.1 | O 0.41 |
| Cholesterol change, mean, mg/dL | Z −9.2 | R −2.1 | P 0.5 | Q 5.3 | O 9.7 |
| Triglyceride change, mean, mg/dL | Z −18.1 | R −2.6 | P 8.3 | Q 19.2 | O 42.9 |

[a]Data from Lieberman et al.[1] and Nasrallah et al.[23]
Abbreviations: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness, O = olanzapine, P = perphenazine, Q = quetiapine, R = risperidone, Z = ziprasidone.

was longest for risperidone (7.0 months) and olanzapine (6.3 months) compared with both quetiapine (4.0 months) and ziprasidone (2.8 months). The overall all-cause discontinuation rate in this pathway was 74%. Olanzapine-treated patients gained the most significant amount of weight: 1.3 lb/month. Patients on ziprasidone treatment lost 1.7 lb/month, while weight changes with both quetiapine and risperidone were negligible. More patients on olanzapine treatment gained more than 7% of baseline weight compared with those taking the other agents. Of the 61 patients who had gained more than 7% of their body weight in phase 1, 42% of those assigned to ziprasidone lost more than 7% of their weight, compared with 20% of those assigned to risperidone, 7% of those assigned to quetiapine, and 0% of those assigned to olanzapine. Olanzapine was associated with the largest increases in total cholesterol and triglycerides, while risperidone and ziprasidone were associated with decreases in both of these parameters. Only risperidone was associated with substantial increases in prolactin levels.

## DISCUSSION

So how are practitioners to utilize the wealth of information from CATIE? Clearly, no one drug is perfect or preferred. Despite decades of intensive research, we are still left with imperfect choices. The fact that at the end of the 18-month study, 74% of the patients in phase 1 were not taking the same drug they started with speaks to these facts: that switching or discontinuation in the maintenance phase of schizophrenia treatment is the rule rather than the exception, and that both patients and clinicians are often dissatisfied with the outcome achieved.

As have many other studies,[26] CATIE has demonstrated the superior efficacy of clozapine. However, agranulo-

cytosis and metabolic and numerous other tolerability and safety problems limit its widespread use. Olanzapine appeared to be somewhat more efficacious than the other medications (possibly due to more optimized dosing), but this positive effect was modest and more than offset by its serious metabolic health complications. In general, the other drugs were equally efficacious compared with each other, although risperidone was somewhat more effective than quetiapine and ziprasidone in the ziprasidone arm of phase 2. Perphenazine did reasonably well, except that because of having the highest neurologic side effects, it could not be used for subjects who had TD at baseline. The suboptimal dosing of some atypicals (especially quetiapine and ziprasidone) remains a nagging issue.

One of the clearest and most compelling messages from CATIE is the issue of metabolic side effects. In a subset of 689 of the 1460 CATIE patients with sufficient metabolic data available, the prevalence of metabolic syndrome was 40.9% by National Cholesterol Education Program (NCEP) criteria, or 42.7% if using the criterion of a fasting glucose threshold of 100 mg/day from the National Heart, Lung, and Blood Institute and American Heart Association (AHA).[27] The rate of metabolic syndrome was higher in female CATIE patients, with 51.6% by NCEP criteria and 54.2% by AHA criteria compared to the male patients (36.0% and 36.6%, respectively). The proportion of women meeting the waist criteria for metabolic syndrome was much higher than the men, at 73.4% versus 36.6%, respectively. The CATIE women were 251% more likely and the men were 138% more likely to have metabolic syndrome compared with a matched control group (without schizophrenia) from the National Health and Nutrition Examination Survey III (NHANES III). This high prevalence of the metabolic syndrome in schizophrenia is further compounded by the very low rates of receiving standard medical treatment for diabetes, hypertension, and hyperlipidemia that have been observed in the CATIE sample prior to enrollment.[23]

Except for clozapine, olanzapine clearly caused the heaviest burden of metabolic side effects. Ziprasidone, on the other hand, was consistently associated with the most benign metabolic side effect profile. Throughout the treatment course, clinicians should remain vigilant to metabolic issues and mindful of the following principles:

- Prescreen all patients for the presence of the 5 risk factors of the metabolic syndrome
- Remain vigilant by regular monitoring during treatment
- Reinforce the need for healthy lifestyle changes such as improved diet and regular exercise
- In drug selection, balance risks versus benefits and minimize iatrogenic risk
- Consider switching to safer alternatives if metabolic parameters worsen during treatment
- Vigorously treat the underlying metabolic disorder when lifestyle or medication changes are not effective enough

Psychiatrists generally spend more time with patients than do internists, and deal with behavioral issues and changes on a regular basis. It is therefore incumbent upon mental health clinicians to help their patients to develop effective coping strategies and lifestyle changes. However, lifestyle changes have proven difficult to establish,[28] and implementing them in an individual with a chronic mental illness is all the more formidable a challenge. Nevertheless, clinicians should be proactive in helping patients to adopt and adhere to effective behavioral habits and treatment regimens.

The CATIE study is reviving the debate about the role of the typical antipsychotics in the overall management of chronic schizophrenia. Although more patients discontinued perphenazine due to extrapyramidal side effects, the increase over other drugs was modest. However, the study was not designed to maximize detection of motor side effects. Perphenazine was modestly dosed, specifically to minimize the risk of extrapyramidal symptoms. In addition, patients with TD, who represent the group of patients most susceptible to iatrogenic neurologic movement disorders, were excluded from assignment to perphenazine. Finally, the length of drug exposure may not have been long enough to detect significant increases in TD.

Prior to the introduction of the atypical agents, extrapyramidal side effects were a major concern of clinicians. This concern has abated considerably with the widespread use of atypical agents, although the metabolic concerns have emerged with some agents. Patients with schizophrenia are at higher risk for development of motor abnormalities. Drug-naive patients with schizophrenia have been shown to manifest abnormalities in the basal ganglia region[29] and also have high rates of baseline extrapyramidal signs.[30] Extrapyramidal symptoms have been correlated with worse treatment outcome, including more negative symptom burden and cognitive dysfunction. Fenton[31] noted that the risk of spontaneous dyskinesias increases with age in antipsychotic-naive patients. The rate was 4% in first-episode patients, 12% in individuals aged less than 30 years who had been ill for several years, 25% for those between 30 and 50, and 40% for those 60 years or older.[31] Atypical antipsychotics tend to have a lower risk of tardive and other movement disorders.[32] The clinician must carefully decide whether the lower cost of the typical antipsychotic is worth the potential striatal neurotoxicity manifested by acute extrapyramidal side effects and long-term TD.

## SUMMARY

With its size, scope, and design, the CATIE study has already established a gold standard for pragmatic research

  

in schizophrenia. CATIE has outlined the challenges faced in selecting from the broad array of treatment options and has revealed the ways in which the clinician must balance therapeutic benefit against the potential harm of various medications to develop the best treatment plan. Above all, treatment must be individualized and optimized, taking into account the patient's medical status, preferences, and psychopathology in the context of the drug's clinical response and side effect profile. CATIE is a landmark study that represents the foundation for many future effective trials in schizophrenia and related psychiatric disorders.

*Drug names:* aripiprazole (Abilify), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), fluphenazine decanoate (Prolixin and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

*Disclosure of off label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

## REFERENCES


1. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223
2. Nasrallah HA, Smeltzer DJ. Contemporary Diagnosis and Management of the Patient With Schizophrenia. Newtown, Pa: Handbooks in Healthcare; 2003
3. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. J Clin Psychiatry 2003;64(suppl 19):6–12
4. Nasrallah H, Korn M. A Rational Approach to Antipsychotic Pharmacotherapy. Medscape Clinical Update-2003. Available at: http://www.medscape.com/viewprogram/2675_pnt. Accessed July 22, 2006
5. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
6. Stahl SM. "Hit-and-run" actions at dopamine receptors, pt 1: mechanism of action of atypical antipsychotics. J Clin Psychiatry 2001;62:670–671
7. Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159–1172
8. Heres S, Davis J, Maino K, et al. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006;163:185–194
9. Treatment for Adolescents with Depression Study (TADS) Team. The Treatment for Adolescents with Depression Study (TADS): demographic and clinical characteristics. J Am Acad Child Adolesc Psychiatry 2005; 44:28–40
10. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028–1042
11. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006;354: 1243–1252
12. Schneider LS, Ismail MS, Dagerman K, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's disease trial. Schizophr Bull 2003;29:57–72
13. Insel TR. Beyond efficacy: the STAR*D trial. Am J Psychiatry 2006;163: 5–7
14. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. Am J Psychiatry 2005;162:836–846
15. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290:1624–1632
16. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003;29:15–31
17. Stroup TS, Lieberman JA, McEvoy JP, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163:611–622
18. Swartz MS, Wagner HR, Swanson JW, et al. Substance use in persons with schizophrenia: baseline prevalence and correlates from the NIMH CATIE study. J Nerv Ment Dis 2006;194:164–172
19. Barry KL, Fleming MF, Greenley J, et al. Assessment of alcohol and other drug disorders in the seriously mentally ill. Schizophr Bull 1995; 21:313–321
20. Nasrallah HA. CATIE's surprises: in antipsychotics' square-off, were there winners or losers? Curr Psychiatry 2006;5:49–65
21. MedLine Plus Drug Information. Phenothiazines: perphenazine. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202457.html. Accessed Aug 5, 2006
22. Jibson M, Glick I, Tandon R. Schizophrenia and other psychotic disorders. Focus 2004;2:17–30
23. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: data from the CATIE schizophrenia trial sample at baseline. Schizophr Res 2006;86: 15–22
24. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005; 19(suppl 1):1–93
25. McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006;163:600–610
26. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158:518–526
27. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005;80:19–32
28. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. J Clin Psychiatry 2003;64: 1308–1315
29. Torrey EF. Studies of individuals with schizophrenia never treated with antipsychotic medications: a review. Schizophr Res 2002;58:101–115
30. Chatterjee A, Chakos M, Koreen A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry 1995;152: 1724–1729
31. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenia. J Clin Psychiatry 2000;61(suppl 4):10–14
32. Tenback DE, van Harten PN, Slooff CJ, et al. for the SOHO Study Group. Effects of antipsychotic treatment on tardive dyskinesia: a 6-month evaluation of patients from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. J Clin Psychiatry 2005;66:1130–1133


  