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# Observations on the CATIE Schizophrenia Study

## How Should the Data Be Translated Into Clinical Practice?

Peter F. Buckley, MD, and Joseph P. McEvoy, MD

A panel of experts met in November 2005 in Washington, DC, to discuss the first published results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study.[1] Participants included several principal study investigators as well as experts in the treatment and management of schizophrenia and bipolar illness. The content of this supplement is based in part on that discussion.

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) is the largest study involving comparative effectiveness of antipsychotic agents ever completed in schizophrenia. Phase I of the study compared treatment of 1460 patients with schizophrenia using five antipsychotic medications: olanzapine, risperidone, quetiapine, ziprasidone, and the first-generation agent perphenazine. The study was initiated by the National Institute of Mental Health in January 2001, and the primary results of phase I were published in September 2005 in *The New England Journal of Medicine.*[1] Baseline data on the prevalence of metabolic abnormalities in this population as well as an estimate of increased risk for cardiovascular disease in these patients have also been published separately. These initial data inform the clinical use of antipsychotic agents in the treatment of schizophrenia and constitute the largest study to date examining metabolic abnormalities in patients with schizophrenia. The panel concluded that the data from CATIE highlight differences among these medications that should assist physicians in matching medication profiles to the needs of individual patients. They noted the high rates of baseline metabolic abnormalities in this patient population and the need to consider the overall health of patients with schizophrenia when making treatment choices. The panel further agreed that CATIE underscored the importance of patient access to all available therapies as key to ensuring optimal outcomes.

Future publications from this extensive study will add to clinical understanding of the use of these medications, including phase I data regarding treatment effects on cognition and cost-effectiveness, phase II results, and further evaluations of the metabolic effects of these medications.

### Design

The goal of CATIE was to compare the overall effectiveness of antipsychotic medications, as indexed primarily by time to discontinuation for any cause and also by key secondary measures.[1] Patients were initially assigned to treatment with perphenazine, olanzapine, quetiapine, or risperidone and followed for up to 18 months. Ziprasidone was introduced to the CATIE trial in January 2002 after approximately 40% of the sample had been enrolled. Comparisons involving the ziprasidone group were limited to the cohort of patients randomized after the addition of ziprasidone (n=889).[1] See **Figure** 1 for the overall design of the trial.

Eligible patients were 18 to 65 years of age and had a diagnosis of schizophrenia. Patients with comorbid conditions such as substance abuse or mood disorders were included. The primary outcome measure of CATIE, all-cause treatment discontinuation, was selected as a metric that integrates efficacy, safety, and tolerability outcomes.[1] Secondary outcome measures are listed in **Table** 1.

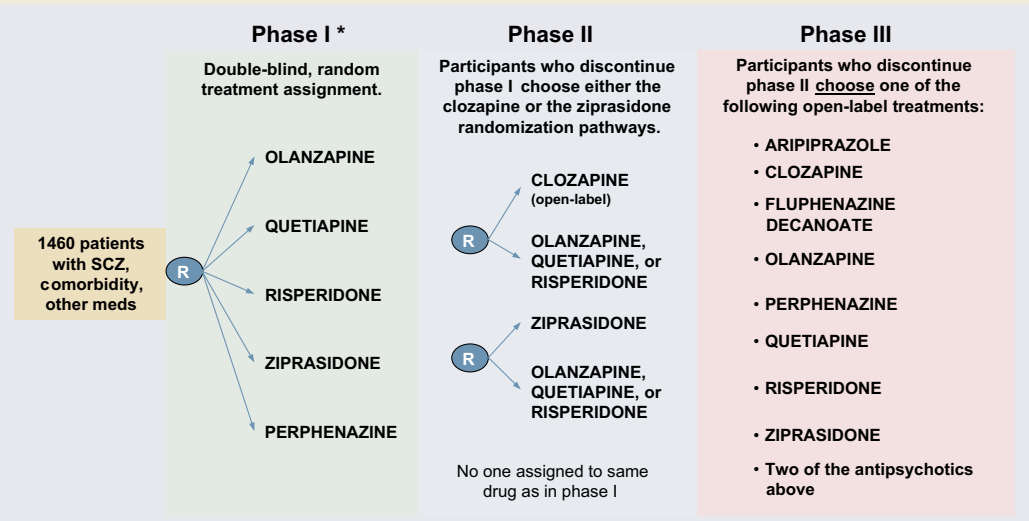
The study design was therefore intended as a practical clinical trial that sought to determine real-world effectiveness

**TABLE 1. Secondary Outcome Measures**

- Psychopathology
- Neurocognitive assessment
- Safety
- Service utilization and costs
- Neurologic side effects
- Adherence to treatment regimen
- Quality of life
- Substance abuse
- Violence/aggressive behavior

**Sources:** Lieberman JA et al,[1] Stroup TS et al,[2] and JP McEvoy, MD, personal communication.

**FIGURE 1. CATIE Schizophrenia Trial Design**




*Phase IA: participants with TD (n=231) do not get randomized to perphenazine; phase IB: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before becoming eligible for phase II.

SCZ = schizophrenia; TD = tardive dyskinesia.

**Source:** Adapted from Stroup TS et al.[2]



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**Art Director:**
Louise A. Koenig

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rather than the more standard approach, which has generally tended to limit the primary end point to the evaluation of efficacy in a more circumscribed study population. Such a design is relatively novel in psychiatry and has been the subject of significant discussion. It was agreed that the primary end point is not a simple measure of efficacy but represents the final outcome of multiple inputs leading to the decision to discontinue (or switch) treatment.

## Overview of Results

Of the 1432 patients who received at least one dose of the assigned study medication, 1061 (74%) discontinued the medication before 18 months for any cause. Although this rate may seem fairly high, it is important to note that a substantial proportion of the patients who discontinued treatment in phase I continued treatment in phase II, where they were switched to another medication. In fact, more than 50% of patients completed the full 18 months of the study, albeit in most cases on a different medication than initially assigned. These results reflect the common occurrence of medication switching in patients with schizophrenia, while also demonstrating the potential for ongoing treatment adherence for most patients.

The percentages of patients who discontinued for any cause were as follows: olanzapine, 64%; perphenazine, 75%; quetiapine, 82%; risperidone, 74%; and ziprasidone, 79%. The time to discontinuation of medication for any cause was longest (ie, most favorable) in the olanzapine group, and the differences were statistically significant for the olanzapine-quetiapine and olanzapine-risperidone comparisons ($P<0.001$ and $P=0.002$, respectively).[1] There was no statistical difference in this measure for olanzapine compared with ziprasidone or perphenazine after adjustment for multiple comparisons.[1] It is important to note that since comparisons to ziprasidone were limited to the cohort of patients randomized after ziprasidone was added (n=889), the statistical power for comparisons involving the ziprasidone cohort was less than that for the other agents in the study.[1] There were no significant differences in time to all-cause discontinuation among the risperidone, quetiapine, ziprasidone, and perphenazine groups.

The CATIE investigators assessed the specific reasons for discontinuation, including lack of efficacy and intolerability. The time to discontinuation due to lack of efficacy was significantly longer in the olanzapine group than that in the quetiapine, risperidone, or perphenazine groups (all $P<0.001$)[1]; there was no statistical difference compared with ziprasidone after adjustment for multiple comparisons. There were no significant differences among the risperidone, quetiapine, ziprasidone, or perphenazine groups.

Comparisons between agents for discontinuation due to intolerable side effects revealed no statistical differences in time to discontinuation, but significant differences in the rates of discontinuation. Olanzapine had the highest rate of discontinuation due to intolerable effects (18%), with half of these discontinuations due to weight gain or metabolic effects. The highest rate of discontinuation due to extrapyramidal effects was seen in the perphenazine group (8% vs 2% to 4% for the other groups).[1]

Although CATIE was not rigorously designed to evaluate cardiovascular effects on the QT interval, there were no substantially different effects of the medications on the corrected QT interval seen on electrocardiography.[1]

- Olanzapine showed significantly greater time to all-cause discontinuation than quetiapine or risperidone
- There were no statistical differences among the risperidone, quetiapine, perphenazine, or ziprasidone groups in time to all-cause discontinuation
- Olanzapine demonstrated the highest rates of discontinuation due to intolerable side effects

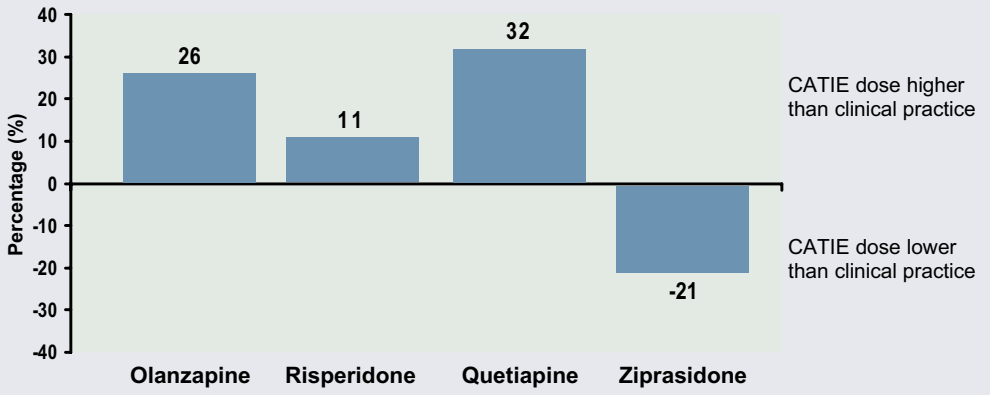
## Dosing

When assessing the clinical applicability of the CATIE findings, one must take study dosing into consideration. Although dose ranges of all the agents were suggested by the study investigators in consultation with the manufacturers, clinical practice regarding optimal doses of these medications have, in some instances, changed since the study was initiated. **Figure 2** shows the differences between mean dose for each drug in the CATIE study and the mean dose currently used in clinical practice. For most agents, mean doses were higher than those currently used in clinical practice, particularly for olanzapine for which the mean modal dose in CATIE was 20.1 mg/day compared with an average of 15.9 mg/day in current clinical practice. The risperidone dose was similar to that used in clinical practice (3.9 mg/day in CATIE vs 3.5 mg/day in current practice). Ziprasidone was the only study agent that was used at a lower dose than is currently standard in clinical practice (113 mg/day in CATIE vs 137 mg/day in current practice) [Verispan (Yardley, Pa.) unpublished data, October 2005].[1]

The panel consensus was that ziprasidone and olanzapine in particular appear to have been dosage outliers from clinical practice, with ziprasidone dosed relatively lower and olanzapine dosed relatively higher than other agents. Also noted was the lack of an explicit requirement to dose study medication with food, which might have affected the ziprasidone group, since food increases

**FIGURE 2. Percentage Differences in CATIE Doses vs Clinical Practice Doses**

Percentages were calculated using the mean modal doses in the CATIE study[1] and the mean doses from current Verispan (Yardley, Pa.) data as of October 2005. The Verispan data may include a higher percentage of inpatients than did the CATIE study.




| | Olanzapine | Risperidone | Quetiapine | Ziprasidone |
|---|---|---|---|---|
| Mean Dose in Clinical Practice (mg/day) | 15.9 | 3.5 | 412.6 | 137 |
| CATIE Mean Modal Dose (mg/day) | 20.1 | 3.9 | 543.4 | 112.8 |

**Source:** Lieberman JA et al.[1]

ziprasidone's absorption substantially (up to twofold).

- Dosing in CATIE was somewhat different from current clinical practice dosing
- Mean modal doses in CATIE were higher for olanzapine and quetiapine and lower for ziprasidone than mean doses used in current practice

## Metabolics

The baseline data from CATIE revealed that rates of metabolic disturbances are even higher than previously thought in this patient population. The panel agreed that this important finding of CATIE has significant public health implications and should impact treatment approaches for patients with schizophrenia.

In an analysis of the CATIE baseline data, McEvoy and colleagues[3] assessed the prevalence of the metabolic syndrome at baseline in 1460 patients in the study. The criteria used to define the metabolic syndrome are shown in **Table 2**. These criteria were derived from the American Heart Association (AHA) definition, which uses a fasting glucose threshold of ≥100 mg/dL to define the metabolic syndrome.

Alarmingly high rates of metabolic abnormalities were observed in the CATIE population at baseline. Seventy-three percent of all women and 37% of all men met the criterion for increased waist circumference (a measure of visceral adiposity). Fifty percent of men and 44% of women met the criteria for hypertension. In the subset of confirmed fasting subjects (n=689), 49% of men and 63% of women had clinically significant baseline high-density lipoprotein cholesterol abnormalities, and 51% of men and 42% of women had fasting triglyceride levels above the metabolic syndrome threshold. Twenty-six percent of fasting subjects had impaired fasting glucose at baseline (≥100 mg/dL), placing them at high risk for the development of type 2 diabetes mellitus.[3]

The overall prevalence of the metabolic syndrome among the fasting cohort of CATIE subjects was 43% (based on AHA criteria) [see **Figure 3**] compared with 24% in a matched control population. (Comparative analyses used an age-, gender-, and ethnicity-matched control sample of subjects randomly selected from the third National Health and Nutrition Examination Survey [NHANES III] database.) The rate of metabolic syndrome in female CATIE subjects was more than twice the rate of metabolic syndrome in the general female population (54% vs 23%, respectively).[3] Despite this high prevalence of baseline metabolic abnormalities, very few patients received medications to treat these conditions during the course of the study. Less than 5% of subjects received glucose-lowering drugs, and less than 5% of subjects received cholestatins (percentages based on the number of patients with data available: 333 olanzapine, 333 quetiapine, 340 risperidone, 259 perphenazine, and 184 ziprasidone subjects).[1]

**TABLE 2. Diagnostic Criteria for the Metabolic Syndrome***

| Risk Factor | Defining Measures |
|---|---|
| Abdominal obesity (waist circumference) | |
| Men | >40 in (>102 cm) |
| Women | >35 in (>88 cm) |
| Triglycerides | ≥150 mg/dL |
| HDL-C | |
| Men | <40 mg/dL |
| Women | <50 mg/dL |
| Blood pressure | ≥130/≥85 mm Hg |
| Fasting glucose | ≥100 mg/dL |

HDL-C = high-density lipoprotein cholesterol.

*≥3 risk factors constitute the metabolic syndrome.

**Source:** Adapted from McEvoy JP et al.[3]

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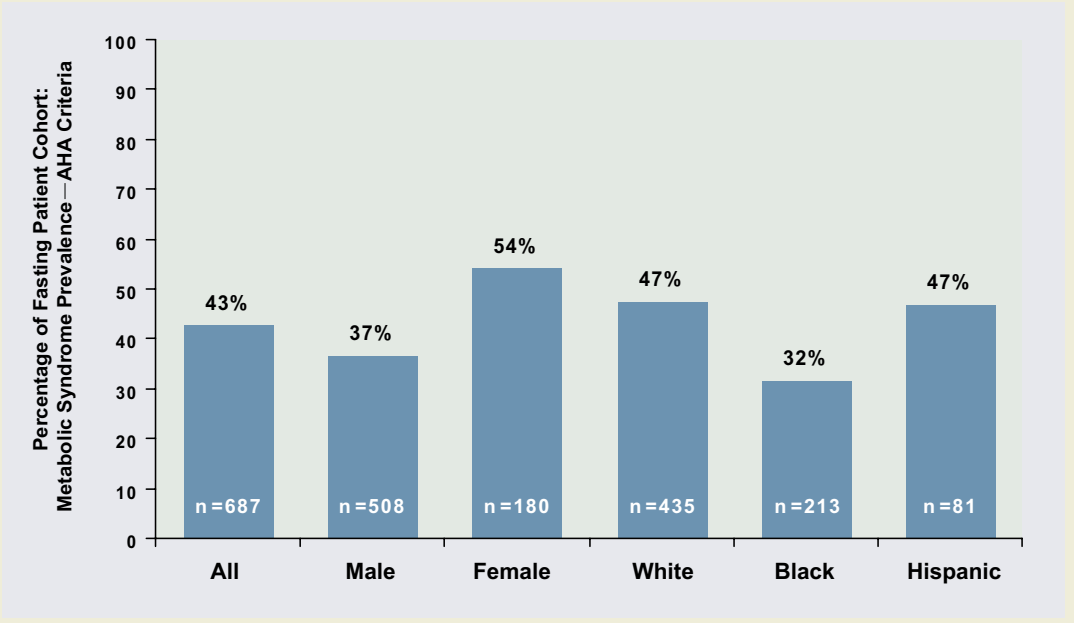
**FIGURE 3. Prevalence of Metabolic Syndrome at Baseline in Fasting CATIE Trial Subjects**




AHA = American Heart Association.

**Source:** McEvoy JP et al.[3]

The potential impact of these abnormalities has been examined using the Framingham coronary heart disease (CHD) risk function to estimate the 10-year risk of developing CHD for patients with schizophrenia. A publication by Goff and colleagues[4] showed male patients with schizophrenia in the CATIE study had a 34% greater risk of developing CHD based solely on their baseline metabolic parameters than did matched controls from the NHANES III database, and women with schizophrenia in the CATIE study had a 50% greater risk of developing CHD than did matched controls.

The impact of the various antipsychotic medications on metabolic measures varied considerably. Olanzapine was associated with substantial weight gain in addition to adverse changes in glucose (as measured by glycosylated hemoglobin levels), cholesterol, and triglyceride levels. Ziprasidone was the only study drug associated with improvement in weight, lipids, and measures of glycemic control.[1]

Given the high rates of metabolic syndrome and abnormalities, considerations of medical health need to be elevated when making treatment choices in this patient population.

- 43% of CATIE subjects had metabolic syndrome at baseline
- Less than 5% of CATIE subjects were treated with glucose-lowering drugs and less than 5% of CATIE subjects received cholesterol-lowering drugs
- Male CATIE subjects had a 34% greater risk of developing CHD and female CATIE subjects had a 50% greater risk of CHD than is seen in the general population

## Clinical Implications of CATIE Phase I

The CATIE trial has provided a wealth of new data regarding the similarities and differences between medications used to treat schizophrenia. Although olanzapine offered some advantages in time to discontinuation, this came at the cost of the highest rate of deleterious effects on weight, lipid levels, and glucose levels. Olanzapine worsened all metabolic parameters over the course of treatment in an already-compromised and at-risk population. The panel thought that this risk-benefit profile should be weighed carefully when making treatment decisions.

Ziprasidone showed effectiveness similar to that seen with risperidone, quetiapine, and perphenazine but was the only agent in the study shown to be associated with improvement in weight, lipids, and measures of glycemic control. Participants noted that given the data showing a high prevalence of metabolic abnormalities in this population, the reduced likelihood for patients to receive adequate medical treatment, and the evidence for differential effects on weight and metabolic parameters, the use of agents like ziprasidone, which carry a favorable metabolic profile, could be considered for patients before significant medical complications arise.

Risperidone showed effectiveness comparable to that of quetiapine, ziprasidone, and perphenazine and showed the lowest rate of discontinuation due to intolerable side effects (10%). Risperidone was, however, the only agent associated with a substantial increase in prolactin levels.

Quetiapine showed effectiveness comparable to that of the other agents except olanzapine.[1] Similar to olanzapine, quetiapine was associated with worsening of all metabolic measures, including weight, glucose, cholesterol, and

triglycerides, although those changes were less severe than those seen with olanzapine. Quetiapine was associated with a significantly higher rate of anticholinergic effects than those observed with the other agents ($P<0.001$)[1].

Perphenazine in this study showed efficacy similar to that of all other agents except olanzapine and was generally well tolerated. Perphenazine was not associated with significantly higher rates of movement disorders than those seen with the other agents, although it did have the highest rate of discontinuation due to extrapyramidal side effects. As the panel noted, the study was not designed to fully examine the relative risk of developing movement disorders, particulary tardive dyskinesia (TD), with perphenazine as compared with the risk of the other agents. Patients with TD were not assigned to perphenazine, and the average time on medication was too short to fully assess the risk of developing TD. The role of perphenazine in the modern treatment of schizophrenia remains unclear.

**Olanzapine**
- Longest time to all-cause treatment discontinuation
- Greatest deleterious effects on metabolic parameters

**Ziprasidone**
- Effectiveness similar to that of risperidone, quetiapine, and perphenazine
- Only agent associated with improvement in weight, lipids, and measures of glycemic control

**Risperidone**
- Effectiveness similar to that of ziprasidone, quetiapine, and perphenazine
- Lowest rate of discontinuation due to intolerable side effects
- Only agent associated with a significant increase in prolactin levels

**Quetiapine**
- Effectiveness similar to that of ziprasidone, risperidone, and perphenazine
- Associated with worsening of all metabolic measures
- Associated with the highest rates of anticholinergic effects

**Perphenazine**
- Efficacy similar to that of risperidone, quetiapine, or ziprasidone
- Highest rate of discontinuation due to movement disorders

The CATIE trial has challenged clinicians to raise the standard of care for patients with schizophrenia. Effectiveness is a composite measure of efficacy, safety, and tolerability. Most clinicians already incorporate this concept in their practices by discussing with patients the relative risks and benefits of the available medications and then matching treatment to individual patient characteristics. With the new data available from CATIE, it is clear that a patient's overall health status—including weight, lipid profiles, and other metabolic parameters—should be a factor in the decision-making process.

## Beyond Phase I

If the initial treatment in phase I was discontinued, the patient moved to the next phase of the study to receive a new treatment. Phase II was designed to have two separate study groups, one for patients who discontinued phase I because of lack of efficacy and the other for patients who discontinued phase I because of lack of tolerability.

Patients who discontinued because of lack of efficacy were randomized to receive either clozapine or a second-generation antipsychotic (olanzapine, quetiapine, or risperidone), testing whether clozapine offered a treatment advantage to those patients. Patients who discontinued their first medication because of tolerability issues were randomly assigned to receive either ziprasidone or another second-generation antipsychotic (olanzapine, quetiapine, or risperidone), testing whether ziprasidone offered a treatment advantage to those patients.[2]

Patients who discontinued their medication during phase II entered phase III for open-label treatment with a variety of medications, either alone or in combination.[2]

## Implications of CATIE Beyond Schizophrenia

It is appropriate for clinicians to be aware of and consider the CATIE data when treating patients in other psychiatric diagnostic categories where there is also evidence for an increased prevalence of metabolic risks. Although a similar assessment of comparative antipsychotic effects in bipolar disorder is not currently available, results from the large Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study will provide insights into the effectiveness of treatments for bipolar disorder.

## Conclusion

The article on CATIE phase I data published in September 2005 in *The New England Journal of Medicine* is an initial report, and all of the data from this study have not yet been released. Publication of data regarding additional key outcomes is anticipated within the next year. These will include effects on cognition and cost-effectiveness data from phase I as well as phase II and phase III results, and dosing issues. Until these results are available, final conclusions regarding comparative outcomes cannot be made.

The results of CATIE undoubtedly will have far-reaching effects that likely will help shape both clinical practice and future studies. CATIE provides the opportunity—and a mandate—for clinicians to reevaluate how they choose pharmacologic treatment regimens for individual patients based on objective evidence. The high rate of metabolic disturbances and low rate of treatment observed in this patient population raise the importance of considering the overall health status of patients with schizophrenia. The data from CATIE support the importance of patients' having access to all available therapies to ensure optimal treatment efficacy.

- CATIE provides evidence to match medication profiles to individual patients' needs
- Access to all available medications is key to ensuring optimal outcomes

## References


1. Lieberman JA, Stroup TS, McEvoy JP, et al, for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005;353:1209-1223.
2. 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.
3. 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.
4. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45-53.



**PARTICIPANTS:**

**Nancy C. Andreasen, MD, PhD**
University of Iowa

**Peter F. Buckley, MD**
Medical College of Georgia
School of Medicine

**John P. Docherty, MD**
Joan and Sanford I. Weill
Medical College

**Susan Essock, PhD**
Mount Sinai School of Medicine

**Richard S.E. Keefe, PhD**
Duke University
Medical Center

**Jeffrey A. Lieberman, MD**
Columbia University College of
Physicians and Surgeons

**Prakash S. Masand, MD**
Duke University
Medical Center

**Joseph P. McEvoy, MD**
Duke University
Medical Center

**Alan J. Mendelowitz, MD**
Albert Einstein College
of Medicine

**Jonathan M. Meyer, MD**
University of California –
San Diego

**Alexander Miller, MD**
University of Texas Health
Science Center

**Henry A. Nasrallah, MD**
University of Cincinnati
College of Medicine

**John W. Newcomer, MD**
Washington University
School of Medicine

**Gary S. Sachs, MD**
Harvard Medical School

**Nina R. Schooler, PhD**
State University of
New York,
Downstate Medical Center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