Practical Applications of Recent Antipsychotic Effectiveness Data

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the planning teleconference series "Practical Applications of Recent Antipsychotic Effectiveness Data," which was held in May and June 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Eli Lilly and Company.*

*The teleconferences were chaired by **Jeffrey A. Lieberman**, M.D., Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York. The faculty were **Phillip D. Harvey**, Ph.D., Mount Sinai School of Medicine, New York, N.Y., **John W. Newcomer**, M.D., Washington University School of Medicine, St. Louis, Mo.; and **Robert A. Rosenheck**, M.D., Yale University School of Medicine, West Haven, Conn.*

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At its introduction in 1989, clozapine—the first and prototype of the "atypical" or "second-generation" antipsychotics—was thought to be a major advancement in the treatment of severe mental illness. Clozapine and the atypical antipsychotics developed in its wake were thought to be more effective and have fewer side effects than the conventional antipsychotics. Although the atypical antipsychotics had fewer neurologic side effects, they had a greater propensity to cause weight gain and metabolic side effects.

The atypical antipsychotics were expected to be more effective, safer, and result in better long-term outcomes. They were also expected to be more cost-effective by reducing the morbidity of the illness, improving patient productivity, and reducing the need for health care services. Unfortunately, this improved cost-effectiveness has not yet been realized. In fact, the cost of treatment for schizophrenia has increased considerably since the use of atypical antipsychotics became widespread.[1]

In this ACADEMIC HIGHLIGHTS, experts in the field of schizophrenia will discuss efficacy and effectiveness data from recent trials. The goal is to help clinicians determine the best possible antipsychotic prescribing practices for patients with schizophrenia.

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

Jeffrey A. Lieberman, M.D., began his presentation by explaining that, despite the preferential use of atypical antipsychotics and the increasing cost of treatment with these medications, the evidence demonstrating their safety and efficacy is limited. To address this issue, the National Institute of Mental Health funded the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project.[2] The CATIE project was designed to compare the effectiveness of conventional and atypical antipsychotics in a real-world setting and with a representative patient sample to directly inform clinical practice.

CATIE Design

Dr. Lieberman described the CATIE project as comprising 3 phases (Figure 1). Patients with schizophrenia (N = 1500) enrolled in phase 1 of the study.[2] Patients were allowed to continue medication treatment for comorbid conditions, but they were asked to discontinue antipsychotic treatment not associated with the study. First-episode patients and treatment-refractory patients were excluded from the study.

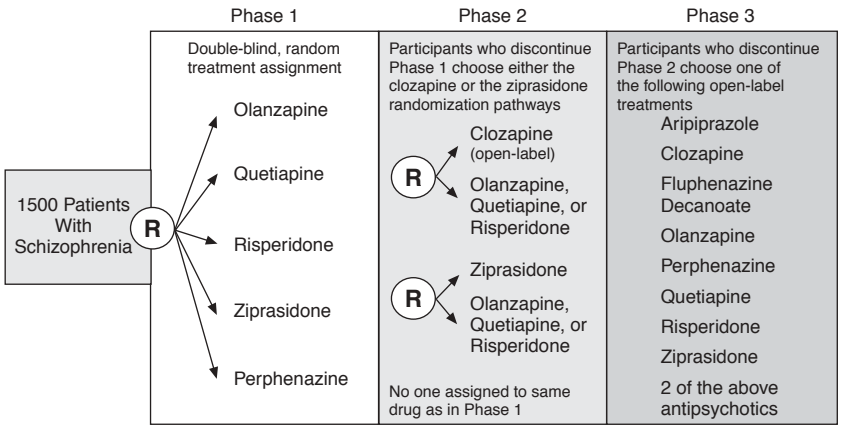
Patients were randomly assigned to atypical antipsychotics olanzapine (7.5–30 mg/day), quetiapine (200–800 mg/day), risperidone (1.5–6 mg/day), or ziprasidone (40–160 mg/day) or the conventional antipsychotic perphenazine (8–32 mg/day).[2] Patients stayed on the medication treatment to which they were assigned for 18 months or until they decided to switch. Patients were allowed to discontinue phase 1 treatment and be randomly assigned to a different medication in phases 2 and 3. This method both simulated clinical treatment and provided long-term outcome data.

Patient-clinician evaluations were used in each phase to determine whether the medication was effective and tolerable.

CATIE Results

Dr. Lieberman summarized the findings of phases 1 and 2 of the CATIE trials.[3]

Figure 1. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial Design[a,b]



[a]Reprinted with permission from Stroup et al.[2]
[b]Phase 1 participants with tardive dyskinesia (N = 231) were not randomly assigned to perphenazine. Participants who failed perphenazine were randomly assigned to an atypical antipsychotic (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.
Abbreviation: R = randomly assigned.

Table 1. CATIE Phase 1 Discontinuation Rates in the Intent-to-Treat Population by Antipsychotic[a]

Variable	Olanzapine (N = 330)[b]	Quetiapine (N = 329)	Risperidone (N = 333)	Perphenazine (N = 257)	Ziprasidone (N = 183)
Dose					
Mean modal, mg/d	20.1	543.4	3.9	20.8	112.8
No. of patients[c]	312	309	305	245	165
Discontinuation, N (%)					
Any reason	210 (64)	269 (82)	245 (74)	192 (75)	145 (79)
Lack of efficacy	48 (15)	92 (28)	91 (27)	65 (25)	44 (24)
Intolerability	62 (19)	49 (15)	34 (10)	40 (16)	28 (15)
Hospitalization for exacerbation of schizophrenia, N (%)	38 (11)	68 (20)	51 (15)	41 (16)	33 (18)

[a]Data from Lieberman et al.[3]
[b]Sample size reflects the number of patients who were included in the final analysis of Phase 1 of the trial.
[c]Number of patients and percentages of patients taking modal dose are based on available data for patients with data on the dose. Information on dose was not available for patients who did not complete the study.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Phase 1. In phase 1, the overall discontinuation rate for all medications was 74%,[3] which was higher than the hypothesized 60%. Of the medications studied, olanzapine had the lowest discontinuation rate (Table 1) but was associated with greater weight gain and increases in measures of glucose or lipid metabolism. Interestingly, the discontinuation rate of perphenazine was lower than that of quetiapine and ziprasidone and only slightly higher than that of risperidone.

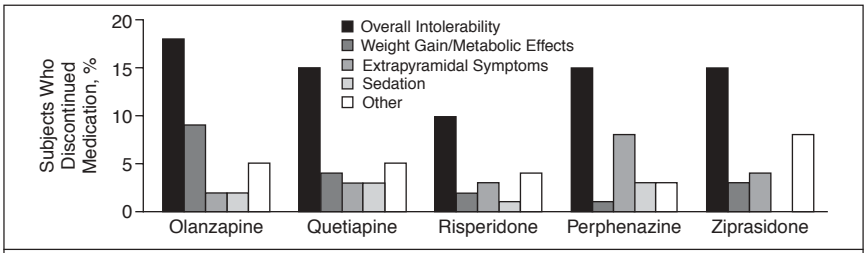
Other outcome measures tracked efficacy and side effects, according to Dr. Lieberman. Efficacy was measured by a change in Positive and Negative Symptom Scale (PANSS) scores every 3 months during the 18-month study. All treatments produced a small initial effect, but only olanzapine showed continued improvement. Extrapyramidal symptoms (EPS) were measured with the Simpson-Angus Extrapyramidal Signs Scale using a very low threshold. The overall percentage of patients exhibiting mild severity was lower than 10%. The propensity of medications to cause weight change was highly variable. A higher percentage of patients in the olanzapine group met the criteria for clinically significant weight gain (≥ 7% body weight) than in the quetiapine and risperidone groups. Again, fewer patients assigned to perphenazine met the criteria for weight gain than those assigned to the other atypical antipsychotics except for ziprasidone, which had the lowest percentage of patients meeting the criteria for weight gain.

Dr. Lieberman noted that the medications produced a similar spectrum of effects in laboratory measures. Olanzapine produced the greatest increase in both glucose and lipid measures, followed by quetiapine. Risperidone increased glucose but not lipid levels. As with weight changes, ziprasidone produced the lowest effect of the antipsychotics on glucose and lipid levels. Risperidone produced high elevations in prolactin, and at the doses given, perphenazine produced negligible elevations in prolactin.

Overall, 15% of patients discontinued treatment during phase 1 owing to intolerability. The leading reasons for discontinuation included weight change and metabolic side effects, extrapyramidal effects, and sedation (Figure 2).[3] Olanzapine had the highest overall rate of discontinuation due to intolerability. Weight gain and metabolic effects were the most widely reported side effects overall and the primary complaints of patients assigned to olanzapine. The highest rate of discontinuation for EPS was in patients taking perphenazine but was only 8%. However, it was twice as high as the next highest rate, which was in patients taking risperidone. Dr. Lieberman explained that the slight differences in side effects are useful guides in matching the individual sensitivities of patients to the side effect profiles of treatments.

Phase 2. Dr. Lieberman briefly shared the results of phase 2 of the CATIE trials. Patients who switched medications in phase 1 because of lack of efficacy were then randomly assigned to either clozapine or one of the atypical drugs they had not received in phase 1. If they discontinued because of intolerability, they were randomly

Figure 2. Subjects of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Who Discontinued Medication Due to Intolerability[a]



[a]Data from Lieberman et al.[3]

assigned to receive either ziprasidone or another atypical medication they did not receive in phase 1.[2]

As with phase 1, there was a high rate of discontinuation in phase 2 of the trials.[4,5] For those patients who discontinued their phase 1 treatment due to lack of efficacy and were assigned to the clozapine pathway, clozapine was associated with a greater reduction in PANSS scores than quetiapine and risperidone but not olanzapine.[5] Clozapine was also associated with a longer time to discontinuation than olanzapine, quetiapine, and risperidone.[4] Fewer patients treated with clozapine discontinued for lack of efficacy than those treated with olanzapine, quetiapine, or risperidone. However, no significant differences were noted among the treatments in time to discontinuation for intolerability.

The CATIE investigators' hypothesis that ziprasidone would be more effective for patients who discontinued their phase 1 treatment due to lack of tolerability was not reflected in the CATIE data.[4] For those patients who discontinued phase 1 treatment for lack of tolerability and efficacy and were assigned to the ziprasidone pathway, risperidone was the most effective in phase 2. For those patients who discontinued phase 1 treatment for a lack of efficacy but not for tolerability, olanzapine was most effective.

Conclusion

Dr. Lieberman concluded that conventional and atypical antipsychotic medications are effective in the treatment of schizophrenia but have significant limitations as reflected by the high discontinuation rates, intolerable side effects, and failure to adequately control symptoms. For treatment-refractory patients, clozapine was shown to be clearly the most effective drug but is underutilized because of its association with serious side effects such as agranulocytosis, seizures, and myocarditis. For patients who are not treatment-refractory, olanzapine was shown to be the most effective, but it was also unfortunately associated with a great side effect burden, including significant weight gain and metabolic changes. Perphenazine, an intermediate-potency conventional antipsychotic, and presumably by extension other intermediate-potency conventional antipsychotics, seemed to be comparably effective and tolerated as atypical drugs.

Treatment for those with schizophrenia must be individualized. There is variation in side effect profiles among drugs that can be matched to individual patients to make treatment more effective. Doctors and patients should carefully evaluate the trade-offs between efficacy and side effects in choosing an appropriate medication.

Factors Influencing Cognitive and Functional Effects Measures

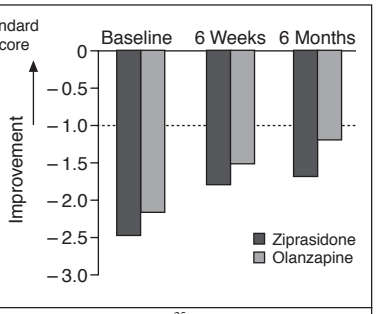
Phillip D. Harvey, Ph.D., stated that several factors affect the potential to differentiate the effect antipsychotics have on cognition. Short-term studies of cognitive enhancement may not give the same answers as longer-term studies, comparative studies yield different results than meta-analyses, changes in functional capacity are difficult to measure, and differences between study populations may have substantial impact on results.

Hagger et al.[6] first reported improvements in cognitive functioning in patients taking clozapine, and these improvements have been reported since then in multiple studies.[7–10] Although atypical antipsychotic medications may be more effective than conventional medications at enhancing cognition, there is very little information about cognitive differing effects of atypical antipsychotic medication.

Implications for Cognitive Change

Depending on how impaired a patient is at baseline, a fixed criterion for functional and cognitive improvement leads to different implications for change. Dr. Harvey explained that more than 1 standard deviation (SD) below the normative range was considered impaired at baseline. An improvement of a full SD in a normally distributed variable can be a 1.9% change (changing from –3 to –2 SD) to as much as a 15% change (–1 to 0, reflecting a change from 1 SD below to the equivalent of the population mean). Use of this criterion may be difficult to implement unless patients start at a specified level of impairment. Dr. Harvey then posed the question: Is it helpful for a patient with an impairment of 6 SDs below normal to improve to 4 SDs below normal? That question may be difficult to answer, since specific functional requirements may be fixed to levels of cognitive performance, and some performance thresholds can have functional significance (improvement in memory span to the point of being able to reliably remember a phone number). The threshold for normality is difficult to define and requires a case-by-case understanding of prior functioning. Implementing criteria for improvement is easiest in patients with specified levels of impairment, which means that

Figure 3: Normatively Derived Change Score for the Global Measure of Cognitive Function at Baseline, 6 Weeks, and 6 Months[a]



[a]Data from Harvey et al.[25]

changes in SDs can be clinically meaningful, even if the patient's function is still impaired.

Patients with schizophrenia have considerable discrepancies between levels of impairment[11] and levels of improvement[12] in episodic memory, executive functions, vigilance, and verbal skills—all critical aspects of cognitive functioning that are relevant to functional outcome. However, the level of improvement with atypical antipsychotics is often not enough to reverse the entire deficit, so patients are left with substantial impairment.

Comparative Studies Versus Meta-Analyses

Dr. Harvey noted that most double-blind studies of atypical antipsychotic medications have used conventional antipsychotics as comparators,[13–21] and most head-to-head studies have compared risperidone and olanzapine to each other[22,23] or to other atypical antipsychotics.[24,25] Few such studies have examined quetiapine[17,19,26] and/or aripiprazole.[26]

A few meta-analyses[12,27] have been conducted on atypical antipsychotics and cognition, but meta-analyses of cognition have limitations. Conceptual combinations (grouping tasks by what they measure) in meta-analyses are problematic because treatment responses differ among tests that measure the same construct in the same study. Because meta-analyses group tasks under conceptual headings such as verbal memory, vigilance, and/or executive functioning, the tasks may not be strongly correlated with each other and may respond differently to treatment, even in the same study with the same patients. For example, one study[28] comparing 3 different Continuous Performance Tests (CPT) showed a correlation between the tests but not enough to consider the 3 versions alternate forms of the same test. Another study[29] using 2 versions of the same CPT showed that the relative difference between risperidone and quetiapine treatment in both studies was similar, with a slight but nonsignificant advantage to risperidone. Dr. Harvey hypothesized that a meta-analysis comparing studies that used 2 versions of the same CPT would show risperidone to be considerably more beneficial than quetiapine.

Is Treatment More Effective on the Beginning Stages of Illness?

Dr. Harvey stated that early intervention with antipsychotic treatment may be beneficial; therefore, first-episode patients might show more improvement than chronic patients. However, it is also possible that chronic patients may show more benefit from treatment with atypical antipsychotics than first-episode patients because of long-term conventional antipsychotic exposure.[12]

Three short-term clinical trials[18,30,31] compared conventional and atypical antipsychotics. In these trials, patients treated with olanzapine[18,30] and risperidone[31] performed better on neurocognitive functioning than those given conventional antipsychotics. More than 50% of treatment-refractory patients who were treated with olanzapine and risperidone experienced clinical improvement on global cognitive scores.[18] In first-episode patients, olanzapine had a small beneficial effect over haloperidol[30] and risperidone was associated with more overall improvement than haloperidol.[31] However, in first-episode patients, the conventional antipsychotic dose was very low, and in the treatment-refractory patients, it was very high, suggesting that any differences between treatments may have been due to dose.

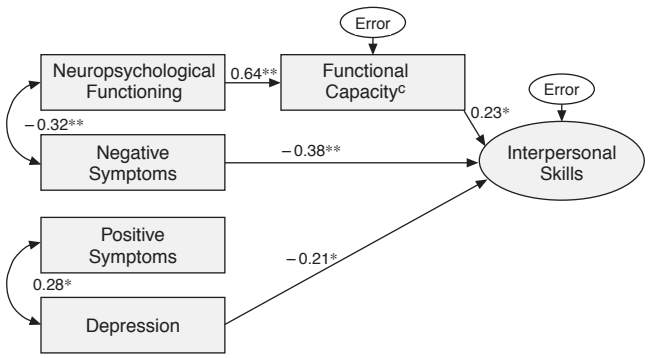
A randomized, double-blind 6-month treatment outcome study[25] that was a continuation of a 6-week efficacy trial[24] examined how much patients improved relative to the normative range during treatment with olanzapine versus ziprasidone. Improvement by at least a half of an SD and less than 1 SD below the normative mean was considered substantial improvement. Dr. Harvey noted that patients entered this study only if they had already clinically responded and were willing to continue in the study and keep taking double-blind treatment. As a consequence, the patients in this study were highly adherent, highly responsive, and not typical of patients one would see in a standard clinical trial.

All variables of cognitive performance improved, showing a normalization of cognitive performance over time ($p < .05$).[25] Improvement continued from baseline to 6 weeks to 6 months. The level of 6-week and 6-month improvement was similar for olanzapine and ziprasidone. The normatively derived change score for the global measure comparing impairment at baseline versus endpoint for patients treated with ziprasidone revealed that a substantial number of patients manifested improvement to the point at which their cognitive functioning was closer to normal over time (Figure 3). Dr. Harvey suggested that subsets of patients can have very different results.

Measuring Functional Capacity

Dr. Harvey stated that cognitive performance has an indirect correlation with functional outcomes. Performance-based assessments are appealing because they are not prone to bias, and there is no need to find patients with informants who can aid in the assessment. One study[29] measured improvement in social cognition, social competence, and cognitive functioning in an 8-week

Figure 4. Prediction of Interpersonal Functioning in the Community[a,b]



[a]Reprinted with permission from Bowie et al.[32]
[b]Model fit: $\chi^2 = 8.22$, df = 9, p = .52; comparative fit index = 0.99.
[c]Measured with the UCSD Performance-Based Skills Assessment.
*p < .05; ** p < .01.

comparative study of quetiapine versus risperidone. The researchers performed a cognitive assessment battery using the performance-based Social Skills Performance Assessment (SSPA) to measure social cognition and social competence, the Trails B assessment to measure motor speed, and the Penn Emotional Acuity Test (PEAT) to measure affect recognition. Episodic memory, executive functioning (social cognition and social competence), and motor speed improved significantly ($p < .05$). PEAT scores did not improve significantly, but performance on the SSPA improved significantly over the course of 8 weeks ($p < .001$).

Quetiapine and risperidone both showed a 20% variance between improvement in executive functioning and episodic memory and social competence.[29] While that overlap was statistically significant, it also meant that 80% of the improvement in social competence was not associated with cognitive improvement. Therefore, while cognitive functioning may be the best available correlate of functional disability in schizophrenia, these results call into question whether it is a strong correlate.

Dr. Harvey noted a critical distinction between competence and performance, and he stressed that this distinction is critical for attempting to enhance social outcomes by changing cognition. A large set of intervening factors is associated with the ability to perform in the real world. For example, personal and familial resources may impact how one actually performs in a way that has little to do with competence. Various factors can either interfere with or facilitate real-world functioning in the context of adequate competence to perform skills.

In order to assess neuropsychological performance by measuring functional capacity and functional outcome, one study[32] used a performance-based assessment of functional capacity called the UCSD Performance-Based Skills Assessment (UPSA), which measures the ability to perform everyday living skills. Clinical ratings on the PANSS and Self Reports of Depression were obtained, and patients' case managers rated their real-world functioning.

Dr. Harvey explained that there were several predictors of interpersonal functioning in the community (Figure 4).[32] Neuropsychological performance was not significantly related to skills-based performance but was mediated by functional capacity. He theorized that negative symptoms and depression are related to interpersonal skills in the community in a way that cannot be mimicked in a laboratory setting. Competence, negative symptom severity, and level of depression all work together to predict the real deployment of skills in the community. For example, treatment that improves functional capacity but worsens negative symptoms may have a potentially deleterious impact on real-world outcomes. Cognitive enhancement alone may not be sufficient to change real-world outcome, so physicians should consider the whole picture of patient functioning.

Conclusion

Dr. Harvey concluded that short-term studies of cognitive enhancement may not provide the same answers as long-term studies and that comparative studies are superior to meta-analysis. Population, treatment, and direct measurement of changes in functional capacity are likely to have a substantial impact on the results. Therefore, cognitive enhancement—particularly with atypical antipsychotic medications—is not a stand-alone phenomenon but is part of the overall picture of the person with schizophrenia and his or her functioning in the world.

Comparing Safety and Tolerability of Antipsychotic Treatment

John W. Newcomer, M.D., explained that some overlap exists between issues of tolerability and safety. Tolerability issues can be defined as time-limited, easily managed, or non–life-threatening. Potential adverse drug effects such as drug-induced parkinsonism, drug-induced prolactin elevation, and sexual dysfunction can be generally categorized as tolerability concerns. Safety issues can be defined as events that occur on an acute or chronic basis that could threaten patients' safety. The risk of myocardial infarction and stroke; metabolic syndrome, an established risk factor for cardiovascular disease and diabetes; diabetes mellitus; and conditions like neuroleptic malignant syndrome or anaphylactic drug reactions are all examples of safety concerns. These two

issues can overlap, however, and tolerability concerns can develop into safety considerations. For example, weight gain can begin as a tolerability problem, but as a risk factor for metabolic syndrome it can increase the risk for life-threatening conditions such as diabetes or cardiovascular disease.

Cardiovascular Risk and Metabolic Risk Factors

Dr. Newcomer stated that tolerability and safety are important issues to consider for a clinician who is prescribing medication for severe mental illness. Patients with schizophrenia have a 40% increased risk of death from medical causes compared with the general population.[33] Cardiovascular disease is the most frequent cause of death in patients with bipolar and unipolar disorder.[34] One study[35] found that standardized mortality ratios (observed deaths/expected deaths) for cardiovascular disease in schizophrenia increased 4.7-fold in men and 2.7-fold in women over a recent 20-year period, making it the leading cause of death in patients with schizophrenia. The increased risk of cardiovascular disease in patients with schizophrenia is likely due to the high prevalence of smoking, obesity, diabetes, and lipid abnormalities in this population.[36] Mortality risk related to medical morbidity in patients with major mental illness is an important focus of concern in the overall management of a patient's health.

Cardiovascular disease. The National Heart, Lung, and Blood Institute (NHLBI)[37] has identified key modifiable risk factors for developing cardiovascular disease (encompassing both coronary heart disease and cerebrovascular disease), which include obesity, smoking, hyperglycemia, hypertension, and dyslipidemia. These risks factors have an additive effect, which means that the development of each additional risk factor further increases the odds of developing cardiovascular disease. Growing evidence[36,38,39] suggests that patients with severe mental disorders such as schizophrenia and bipolar disorder have an increased prevalence of key cardiovascular risk factors, which could explain the observation of higher rates of cardiovascular disease in the mentally ill population (Table 2).[40]

Obesity. Obesity is an important predictor of cardiovascular disease and also a contributor to other modifiable risk factors such as diabetes and dyslipidemia. Men and women with a high body mass index (BMI) are at an increased risk of morbidity and mortality, especially death from cardiovascular disease.[41] Compared with men and women with a BMI of 21, men and women with BMI of 26 have a risk factor that is 4 to 8 times higher, respectively.[42] The risk of medical conditions such as hypertension and cholelithiasis is also higher in men and women with a BMI of 26 compared with leaner men and women.

Increases in adipose tissue mass are associated with decreases in insulin sensitivity,[43] which initially results in a compensatory increase in secretion of insulin by the pancreas. This compensatory mechanism can eventually fail in persons at risk for type 2 diabetes, leading to hyperglycemia. However, even prior to hyperglycemia, hyperinsulinemia and insulin resistance increase the risk for development of the insulin-resistance syndrome, which includes a variety of physiologic changes including disturbances in glucose metabolism, uric acid metabolism, and lipid metabolism. The dyslipidemia associated with insulin resistance syndrome includes increases in fasting plasma triglyceride, decreases in high-density lipoprotein (HDL) cholesterol, and atherogenic changes in low-density lipoprotein (LDL) cholesterol. In addition, insulin resistance syndrome is associated with hypertension, increased inflammatory markers, and an increased risk of blood clotting. All of these are risk factors associated with cardiovascular disease.[44,45]

Diabetes mellitus and cardiovascular risk. Insulin resistance characteristically precedes the onset of type 2 diabetes.[46] Vascular function is important in the prevention of cardiovascular disease, and insulin directly affects vascular endothelium and smooth muscle.[45] However, insulin-resistant conditions such as type 2 diabetes and obesity are associated with vascular dysfunction. Obesity, insulin resistance, and endothelial dysfunction coexist not only in people with type 2 diabetes but in other groups at risk for cardiovascular disease, such as those individuals with glucose intolerance, hypertension, and dyslipidemia.[44,47]

Table 2. Estimated Prevalence of Cardiovascular Disease Risk Factors Among Patients With Schizophrenia or Bipolar Disorder[a]

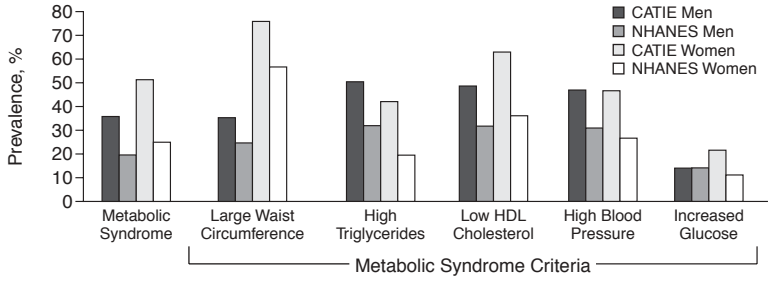
Modifiable Risk Factors	Estimated Prevalence (%)	
	Schizophrenia	Bipolar Disorder
Obesity	42.0	20.8–49.0
Smoking	54.0–75.0	54.0–67.6
Diabetes	13.0–14.9	8.0–17.0
Hypertension	19.0–57.7	35.0–39.0
Dyslipidemia	25.0	23.0

[a]Reprinted with permission from Newcomer.[40]

Within the U.S. National Cholesterol Education Program (NCEP),[48] diabetes was initially considered a risk factor but is now considered a risk equivalent for cardiovascular disease. Haffner et al.[49] have reported that patients with diabetes but without a previous myocardial infarction have a risk for myocardial infarction that is equivalent to that of patients without diabetes who have already experienced a previous myocardial infarction. Patients who were nondiabetic with no prior myocardial infarction had the lowest incidence of myocardial infarction (3.5%), while patients who were diabetic with a previous myocardial infarction had the highest rate (45%).

Metabolic syndrome. The NCEP defines metabolic syndrome as a constellation of lipid and nonlipid risk factors of metabolic origin, closely related to insulin-resistance. Dr. Newcomer noted that a diagnosis of metabolic syndrome enhances the risk for cardiovascular disease.[48] According to the NCEP, metabolic syndrome diagnosis involves identifying in a patient 3 or more of the criteria outlined by the NCEP Adult Treatment Panel III, which includes abdominal obesity,

Figure 5. Comparison of Metabolic Syndrome and Individual Criterion Prevalence in Fasting Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Subjects and Matched National Health and Nutrition Examination Survey (NHANES III) Subjects[a,b]



[a]Data from McEvoy et al.[58]
[b]$p \leq .001$ for all values except glucose criterion: $p \leq .9635$ (men) and $p \leq .0075$ (women).
Abbreviation: HDL = high-density lipoprotein.

high triglyceride levels, low HDL levels, high blood pressure, and high fasting glucose levels. People with metabolic syndrome have a 1.37 to 2.01 hazard ratio[50,51] and 1.5 to 3.0 relative risk[52,53] for cardiovascular disease and a 3.5 hazard ratio[54] and 1.3 to 4.2 odds ratio for diabetes.[46,55,56] The risk for coronary heart disease increases as the number of metabolic syndrome criteria increases.[54,55]

Medical Risk in Severe Mental Illness

According to the third National Health and Nutrition Examination Survey (NHANES), the metabolic syndrome is present in 23.7% of the U.S. population.[57] Using the NCEP criteria for metabolic syndrome, McEvoy et al.[58] found that the prevalence for metabolic criteria in subjects entering the CATIE study who had received prior treatment was 40.9%, which is almost twice that of an age-matched general-population NHANES comparison group. Based on prevalence of individual criteria in this study, women with schizophrenia were at a 140% greater risk and men with schizophrenia were at an 85% greater risk of metabolic syndrome than the age-corrected general population sample. Compared with the NHANES group, patients with schizophrenia had a higher prevalence of almost all criteria for metabolic syndrome (Figure 5).[58] The only exception was that men with schizophrenia entering the CATIE study had a prevalence of abnormal fasting blood glucose similar to their NHANES counterparts. Dr. Newcomer explained that, in general, compensatory hyperinsulinemia can initially buffer changes in plasma glucose, so that glucose control can be maintained for some years before developing into frank diabetes mellitus, even when changes in BMI, plasma lipid levels, and blood pressure are present.

Arguably, the most important modifiable risk factor associated with metabolic syndrome is obesity. In the United States, 27% of the general population is obese compared with a reported 42% of patients with schizophrenia[39] and 49% of patients with bipolar disorder.[59] Psychotropic drugs prescribed to patients with schizophrenia or bipolar disorder can exacerbate or induce modifiable risk factors associated with cardiovascular disease or metabolic syndrome.[60]

Dr. Newcomer discussed a recent meta-analysis[61] that examined the relationship between diabetes risk and atypical antipsychotic use. Summary odds ratios were computed for groups treated with clozapine, olanzapine, risperidone, and quetiapine were compared with odds ratios in groups treated with conventional antipsychotics and those that received no treatment. Groups treated with clozapine or olanzapine had a significantly increased risk of diabetes compared with conventional antipsychotics and no treatment. No substantial increase in risk was associated with groups treated with quetiapine or risperidone compared with those treated with conventional antipsychotics or receiving no treatment.

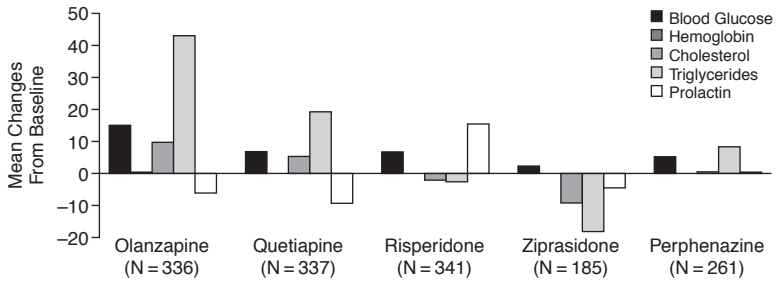
Impact of Data From the CATIE Trial

Dr. Newcomer explained that changes in metabolic risk were observed in data from the CATIE study described by Dr. Lieberman.

Weight gain. Results from phase 1 of the CATIE trial[3] were consistent with data from previous studies, indicating that different antipsychotics carried a different magnitude of risk for inducing clinically significant changes in weight. Olanzapine treatment produced the greatest mean increase in weight (9.4 lb [4.2 kg] or approximately 2 lb per month of treatment), while ziprasidone and perphenazine produced a mean decrease in weight (–1.6 lb [–0.72 kg] and –2.0 lb [–0.9 kg], respectively). However, Dr. Newcomer noted that decreases in weight observed in some treatment arms in this study most likely resulted from the removal of effects produced by the prior medication rather than an intrinsic weight-lowering effect of the antipsychotics under study.

Laboratory measures. The change in plasma variables during the treatment arms of phase 1 is best evaluated by examining exposure-adjusted mean values (Figure 6).[3] Changes in plasma glucose did not differ across treatment arms, but changes in glycosylated hemoglobin values did differ significantly ($p = .01$) across treatment conditions, with olanzapine treatment producing the largest increases. Dr. Newcomer reiterated that, because changes in glucose tend to be buffered by changes in insulin, plasma glucose may not be the most sensitive indicator of treatment-related changes in insulin resistance and metabolic risk over a study of this duration. In contrast, plasma triglyceride levels varied significantly ($p < .001$)

Figure 6. CATIE Phase 1 Change From Baseline in Laboratory Values (Exposure-Adjusted Means) in the Intent-to-Treat Population by Antipsychotic[a]



[a]Data from Lieberman et al.[3]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

across the different antipsychotic treatments, and cholesterol levels followed a similar pattern. The changes in plasma triglyceride levels were clinically significant. Increases in fasting plasma triglyceride are an indicator of insulin resistance, and increases in either fasting or nonfasting plasma triglyceride are associated with cardiovascular risk. CATIE patients randomly assigned to olanzapine had the largest increase in plasma triglyceride. The ziprasidone treatment arm was the only condition associated with an improvement in all metabolic measures.

Plasma prolactin changes differed across treatments, with risperidone associated with the largest increases in prolactin levels (15.4 ng/dL). Perphenazine was the only other medi cation that showed an increase in prolactin levels (0.4 ng/dL). Differences among medications in the change in corrected QT intervals were not observed in this study.[3]

Switching medication. When switching medications, the amount of weight change observed can depend on the characteristics of both previous medication and the medication to which patients are switched. For example, switching from a high-potency conventional antipsychotic that is associated with little weight gain to another low-risk medication with respect to weight gain may not yield significant changes in weight. However, switching from medication with a high risk of weight gain such as olanzapine to a medication with lower risk such as ziprasidone or aripiprazole can be associated with weight loss. The same principle may apply to changes in lipids during antipsychotic treatment. Ziprasidone is not a lipid-lowering agent, but patients randomly assigned to ziprasidone in the CATIE study showed a decrease in plasma triglyceride.[3] Observations like this contribute to the interpretation that the cause of the decrease is the removal of an effect of the previous treatment. Long-term open-label study data from Weiden et al.[62] on switching medications present a similar pattern. Significant weight loss and lipid reductions were observed in patients switching to ziprasidone from olanzapine but not from conventional antipsychotics.

Conclusion

According to Dr. Newcomer, the CATIE data contribute additional support to the conclusion expressed in the consensus statement from the American Diabetic Association, American Psychiatric Association, and other organizations[63] that there is a differential risk of weight gain across the atypical antipsychotics and evidence of increased risk of hyperglycemia and dyslipidemia associated with olanzapine and clozapine treatment. The ADA consensus statement concluded that there was discrepant evidence regarding risk for diabetes and dyslipidemia during risperidone and quetiapine treatment and no evidence of risk for diabetes or dyslipidemia associated with aripiprazole or ziprasidone treatment.

Dr. Newcomer voiced a growing concern among clinicians regarding the level of medical care received by psychiatric patients, including those with identified chronic conditions such as diabetes.[64] Clinicians should anticipate medical comorbidity and perform routine screening in an effort to improve quality of care for persons with mental health conditions. Even small improvement in any one of the modifiable risk factors discussed can decrease cardiovascular disease risk.[65]

Dr. Newcomer concluded that treatment with psychotropic agents is associated with a variety of side effects that can range in significance from minor tolerability concerns to major safety issues. Individuals with schizophrenia and other major mental disorders have an increased prevalence of key modifiable risk factors that increase morbidity and mortality from a variety of medical conditions. These conditions are important to consider when assessing and monitoring side effects associated with psychotropic therapy. Importantly, psychotropic medications can impact some of those risk factors, including potential medication effects on body weight and adiposity. Principles of primary prevention suggest the importance of lowering risk for disease by using monitoring and intervention approaches that can be tailored to psychiatric patient populations.

Cost-Effectiveness Measures, Methods, and Policy Implications From the CATIE Trials

Robert A. Rosenheck, M.D., began his presentation by stating that the atypical antipsychotics have expanded rapidly as a treatment for schizophrenia as well as for other psychiatric illnesses. Prescriptions for antipsychotic medications have increased over the past decade[66,67] as the atypical antipsychotics have replaced conventional antipsychotics. Shifting to newer medications was expected to reduce cost in

other areas of health care for people with schizophrenia.[68] However, available data suggest that Medicaid spending on antipsychotic medications actually increased by 610% as doctors have shifted to the more expensive atypical antipsychotics, and spending in other areas of mental health and medical care has not declined.

In 2005, domestic sales of all antipsychotics in the United States alone totaled $10.5 billion; atypical antipsychotics accounted for 92% of this total.[69] These substantial costs have drawn the attention of administrators and benefit managers as well as clinicians and consumers who pay for their medications out of pocket. Since most of the cost of these medications is funded through Medicaid, it is natural to consider their cost effectiveness. Dr. Rosenheck stated that it is possible to test the cost effectiveness of a medication program by comparing its benefits with its costs; if the benefits outweigh the costs, then the program deserves to be implemented. If a program costs more than the total of its benefits, then implementation of the program is not rational.

Challenges to Testing Cost Effectiveness

Dr. Rosenheck noted, to start, that testing cost effectiveness presents substantial methodological challenges. First, it is difficult to measure health states precisely and even more difficult to attribute monetary values to them. Secondly, when costs are evaluated, they must be considered comprehensively. Whereas some parts of society such as outpatient health systems will pay more as they use these medications, other parts of society such as the hospital systems, the criminal justice system, or the homeless service system may actually be benefiting from more effective medications and paying less.

Another challenge to testing cost effectiveness is the false assumption that atypical antipsychotics are a homogenous group that can be compared with conventional antipsychotics on measures of efficacy. A meta-analysis by Davis et al.[70] revealed that only 4 of 10 available atypical antipsychotics studied produced substantially greater benefits than conventional antipsychotics. Of the atypicals, only clozapine had even a moderate effect size (0.49), whereas amisulpride, olanzapine, and risperidone produced small-to-moderate effects (around 0.20 to 0.25 effect size).[70] These results suggested that only 4 of the 10 studied atypical antipsychotics are even moderately superior to conventional antipsychotics and that the magnitude of the effects are substantial only for clozapine, which is used in less than 5% of patients with schizophrenia.[71]

Cost Effectiveness From CATIE Trials

The CATIE trial was designed to evaluate the effectiveness, side effects, costs, and the cost effectiveness of selected antipsychotic medications. The primary outcome of the CATIE study was time to all cause–discontinuation, or the length of time patients stayed on their medications before switching to another medication. The initial report of the CATIE trial[3] did not address the issue of total health care costs or present paired symptom comparisons between the medications, nor did it present measures of quality of life or make estimates of overall cost effectiveness. The cost-effectiveness component of CATIE focused on a comparison of initiation strategies. Dr. Rosenheck explained that the goal was to determine whether starting treatment with one medication would result in better outcomes and lower costs than starting on therapy with another medication over the entire duration of the trial.

Cost-effectiveness methods. The methods for cost and effectiveness measurement and analysis in CATIE[2] followed as closely as possible the recommendations set forth by the Public Health Services Task Force on cost effectiveness in health and medicine.[72] A dominant choice is an agent that is significantly both less expensive and more effective than other agents. A weakly dominant choice is an agent that is clinically superior or is less costly and that is no worse on the other dimension than other agents. For more expensive and more effective agents, the incremental cost-effectiveness ratio is calculated (difference in cost/difference in effectiveness).

Measuring cost. The first component of measuring cost effectiveness is quantifying total costs. CATIE investigators documented use of a broad range of inpatient, outpatient, psychosocial, and rehabilitation services with every patient, every month, and then used both the published literature and administrative data from a variety of sources to determine the unit cost of each of these services.[2] Some examples of such unit costs include the cost of each day of hospital care, each outpatient visit, and each psychosocial rehabilitation service. Service use (type and number of units used) was measured through monthly interviews with study participants. Drug costs were evaluated by protocol prescription records as well as by patient reports of all nonstudy medications, including psychotropics and general medical prescriptions. The costs of study drugs were based on published wholesale drug prices with adjustments for Medicaid and Veterans Health Administration (VA) discounts and rebates. The costs of all other medications were estimated on the basis of prescription cost data from the MarketScan database, which is a large sample of prescription records from managed care corporations.[73]

Dr. Rosenheck explained that it is important to take nuances of medication costs into account. For example, based on wholesale prices for medications,[74] average monthly drug costs for patients treated in CATIE were $451 per month. Based on discounts and rebates,[75] the average monthly costs were only $386—85.7% of that total. If all patients sampled had received the Medicaid prices, monthly costs would have been lowered to $345/month, and if all patients had received VA prices—which are the lowest available—the costs would have been only $268/month.[76]

Measuring effectiveness. Treatment effectiveness in the cost-effectiveness analysis in CATIE was measured in 5 ways: the PANSS,[77] quality adjusted life years (QALYs),[78] patient weighted preferences,[79] the Visual Analog Scale,[78] and the key item from Lehman Quality of Life questionnaire.[80] The PANSS was used to examine symptom scores so that the results of CATIE could be readily compared with the results of previous studies. The primary outcome measure in the cost-effectiveness analysis was a health state utility assessment measured in QALYs.[72,78] CATIE benefited from a recent series of methodological studies[78] that demonstrated a systematic method for using PANSS data and indicators of side effects to derive health state assessments in QALYs. The resulting measure, which was the primary outcome in the cost-effectiveness analysis of CATIE, combined measures of symptoms and measures of centrally important side effects to present an overall measure of well-being, as assessed by representatives of the general public.

Individual patient preferences were also evaluated at each assessment time point in CATIE by asking participants what areas of improvement were most important to them.[79] The outcome was measured by the priority that each patient put on each of 6 domains including symptoms, cognitive ability, side effects, energy, social relationships, and employment. The resulting patient-weighted preference index[79] thus incorporated a full range of outcomes weighted according to how important they were to each patient at the time of each assessment. The Visual Analog Scale[78] and the Lehman Quality of Life scale,[80] global measures of quality of life, were also used to evaluate patient-assessed health and well-being.

Potential Implications of Cost-Effectiveness Analysis

Dr. Rosenheck, referring to the at that time unpublished cost-effectiveness analysis of CATIE data (subsequently published[81]), emphasized potential implicaitons of this analysis. First, one of the strengths of cost-effectiveness analysis is that it is an analytic technique for combining outcome and cost data that allows researchers to characterize the probability of a given value of each different treatment outcome for an overall population. Although cost-effectiveness analysis cannot determine what the precise costs and benefits would be for any individual patient, it does provide an independent and unbiased evaluation of treatment value.

Secondly, Dr. Rosenheck stressed that although cost-effectiveness analysis does not by itself promote models of clinical care or health care policy, it does provide one kind of scientific input for the policy process. Cost-effectiveness analysis is one of the most inclusive types of analysis involved in research because it incorporates costs, effectiveness, and side effects in an integrated and quantified assessment of health care value. Cost effectiveness is not necessarily the most important ingredient in shaping either clinical practice or public policy. Dr. Rosenheck stressed that individual treatment decisions should come out of the personalized dialogue of doctor and patient, while public policy must ultimately be based on the considered judgments and interactions of all relevant stakeholders.

Policy Alternatives

The crucial decisions that may come out of a cost-effectiveness analysis involve the application of "the cost-effectiveness test" and the determination of whether constraints on provider behaviors can be implemented to limit costs without unduly limiting health benefits or patient choice.

What potential policy alternatives might come out of the CATIE study? Dr. Rosenheck outlined 4 approaches to dealing with medication costs: (a) make all medications equally available to all patients (open formulary); (b) develop a tiered formulary with different costs for i) generic, ii) preferred patent medications, and iii) other patent medications; (c) set a priority stepped sequence for drug delivery; and (d) restrict reimbursement for some costly medications through mechanisms such as prior authorization or closed formularies.

Research on tiered formularies in the delivery of psychotropic medications[82] has suggested that these strategies can be implemented without imposing any limitation on access for patients unless total prices go up. The use of a tiered formulary does not seem to reduce access to medications as long as the cost of the most inexpensive medications does not increase. However, no research exists to date on the use of tiered formularies with antipsychotic medications, and the application of such a formulary would need to be justified by a full consideration of research findings and prospective monitoring.

A priority sequence for antipsychotic treatment would maximize choice but create general incentives for less expensive, equally safe, and effective medications. Such an approach offers a lower price for the first recommended medication in a predetermined sequence but standard prices for subsequent medications if the first one failed. More expensive medications in this stepped approach would be offered at discount prices only if a patient has already tried and failed the cheaper drug and thus has a demonstrated need for the more expensive medication.

Dr. Rosenheck suggested that the tiered formulary and the priority sequence stepped approaches would apply only in situations in which consumers pay out of pocket for their medications. Since many patients with schizophrenia or other serious mental illnesses receive their medications from Medicaid or other public insurance programs, tiered formulary programs might not apply. In public insurance programs, price constraints could be imposed administratively through 2 options, although there are others: One option would be a stepped policy, which would administratively require people who need to change medications to try a less expensive but equally safe and effective drug before a more

expensive drug. Another option would require an administrative review or prior authorization in which physicians are at liberty to prescribe more expensive medications if they are warranted but must provide justification for the use of such medications.

Conclusion

Dr. Rosenheck concluded by stating that the ultimate goal of cost-effectiveness analysis is to optimize the use of societal resources to maximize the public health. For consumer goods such as clothing, housing, and motor vehicles, the market serves well to produce a beneficial distribution of resources. The market mechanism, however, does not work well in the area of health care because consumers often do not have all the medical information needed to decide what is best for them. In such cases, expert knowledge based on research and clinical experience should be a guide to optimal treatment. Cost-effectiveness analysis can help guide such decisions because, in the absence of the price mechanism, biases can influence resource allocation in ways that result in poor use of limited societal resources.

Atypical antipsychotics have become the most costly single pharmacologic item in the Medicaid program and one of the most costly health care investments that our society makes each year. Dr. Rosenheck expressed hope that when fully analyzed and published, the results of the CATIE study will inform clinical and policy decision-making in such a way as to optimize the well-being of people with schizophrenia, their families, and the general public.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The chair 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 activity.

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