Antipsychotic Safety and Efficacy Concerns

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Treatment for schizophrenia has evolved considerably since antipsychotic agents were introduced in the 1950s, with atypical antipsychotics supplanting the use of first-generation antipsychotics over the past decade. Despite the widespread belief that the atypical antipsychotics are superior to the conventional antipsychotics, clinicians lack compelling evidence about whether these new drugs really are safer or more effective than the older alternatives, or whether some atypical antipsychotics may be more effective than others. Both the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1) sought to determine if atypical antipsychotics were truly safer and more effective than typical antipsychotics, but the evidence provided did not support the superiority of the atypical antipsychotics as expected. However, differences between atypical antipsychotics and typical agents may accrue over time, and the 2 trials may not have had a sufficient duration to determine this benefit. Long-term studies greater than 1 year may provide data to support the belief that atypical antipsychotics are more effective treatments for long-term safety and prevention of relapse in schizophrenia than older agents. While atypicals do have lower incidences of extrapyramidal symptoms and movement disorders than conventional antipsychotics, concerns about these adverse effects have been replaced by concerns about metabolic side effects. Given the widespread use of atypical antipsychotics, the psychiatric community has come to recognize that monitoring of metabolic side effects is the new standard of care for treating severely mentally ill patients. *(J Clin Psychiatry 2007;68[suppl 14]:20–26)*

Treatment for schizophrenia has evolved considerably since antipsychotic agents were introduced in the 1950s. The last decade has seen the introduction of a new class of treatments, the atypical antipsychotics, and these drugs have quickly overtaken use of first-generation antipsychotics. Despite the widespread belief that atypical antipsychotics are superior to typical antipsychotics, clinicians lack compelling evidence about whether these new drugs really are safer or more effective than the older alternatives or about whether some atypical antipsychotics may be better than others.

CATIE AND CUtLASS 1

Recently, 2 large, pivotal trials sought to clarify these issues. Both the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[1] which was sponsored by the National Institute of Mental Health, and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1),[2] which was funded by the Health Technology Assessment Program of the United Kingdom National Health Service, compared typical and atypical antipsychotics to determine if the atypical antipsychotics are more effective, and if the higher cost of the atypicals is justified by improved outcomes. The CATIE researchers selected time to all-cause discontinuation as the primary outcome measure, based on the rationale that time to discontinuation is a clinically meaningful outcome that reflects efficacy, side effects, and the input of both patients and clinicians.[1] The CUtLASS 1 study used total score on the Quality of Life Scale (QLS), which measures functioning in a number of key areas such as interpersonal relationships and occupational role, as the primary outcome measure.[2]

Prior to the CATIE and CUtLASS 1 trials, existing trials had a number of shortcomings.[1] These shortcomings included the short-term nature of most studies, with durations that were inadequate to determine long-term effectiveness and cost issues, and enrollment criteria that generally excluded those with comorbid conditions or those who were taking concomitant medications and thus did not reflect the types of patients encountered in real-world clinical situations. The CATIE study was planned to evaluate antipsychotic drug effectiveness for at least 18

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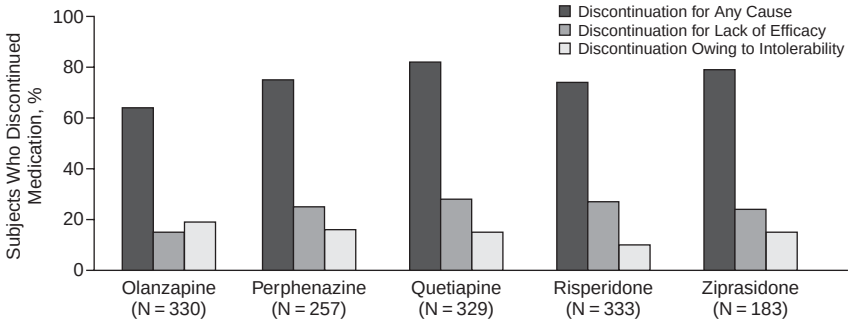
Figure 1. Percentage of Subjects Who Discontinued Treatment in CATIE Phase 1[a]



[a]Data from Lieberman et al.[5]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

months,[1] and the duration of the CUtLASS 1 study was 1 year.[2] Moreover, both CATIE and CUtLASS 1 used broad inclusion criteria to reflect patients seen in clinical practice.[1,2]

In the CATIE trial, the basic criteria for inclusion were that patients had to be 18 to 65 years of age, have a diagnosis of schizophrenia (but not schizoaffective disorder), and not be experiencing their first episode of schizophrenia or have treatment-refractory schizophrenia.[1] Since the CATIE investigators sought to enroll subjects with real-world profiles, individuals with medical or psychiatric comorbidities were only excluded if it would be unsafe to randomly assign them to one of the treatments. The study population in the CUtLASS 1 trial differed from that of CATIE in that many of the participants who entered the study had been taking typical antipsychotics. Enrollment criteria for CUtLASS 1 included age of 18 to 65 years; diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder; and at least 1 month since the first onset of positive psychotic symptoms.[2] Also, a decision by the patient's psychiatrist to change the patient's medication due to either inadequate clinical response or intolerability was required to enter the trial.

In the first phase of CATIE, patients were randomly assigned to receive either the typical agent perphenazine or 1 of the following atypical antipsychotics: olanzapine, quetiapine, risperidone, or ziprasidone (once it became available).[1] Individuals with tardive dyskinesia at baseline were not entered into the perphenazine arm. Although the primary outcome measure was time to all-cause discontinuation, the study was designed to measure key causes of discontinuation and associated measures of effectiveness and safety.

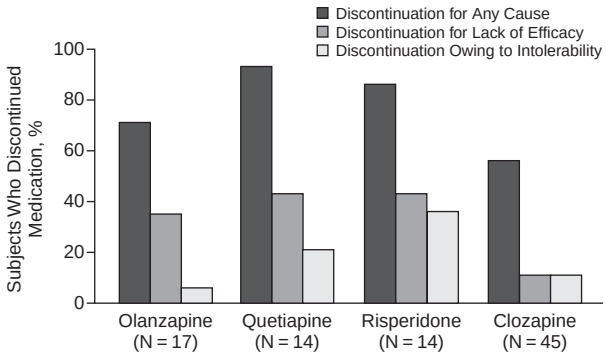
In the CUtLASS 1 study, patients were randomly assigned to receive either a conventional or atypical antipsychotic, and the consultant psychiatrists were responsible for selecting the individual drug in each class prior to randomization.[2] Although the primary outcome measure was total score on the QLS, the study also looked at a number of secondary outcome measures including scores on the Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for schizophrenia, Global Assessment of Functioning scale, and adverse effects scales.

Each of these studies[1,2] discovered valuable information regarding treatment with various antipsychotics, but they did not provide evidence to support the superiority of the atypical antipsychotics as a class compared with typical antipsychotics as had been expected. One hypothesis is that the efficacy differences between conventional and atypical antipsychotics (excluding clozapine) are modest. However, an alternative hypothesis is that the differences between antipsychotics may accrue over time. Although the CATIE and CUtLASS 1 studies indicated high levels of efficacy and response for both typical and atypical antipsychotics, these trials may not have had long enough duration to reveal safety and efficacy advantages of the atypicals. Very few relapse-prevention trials have shown advantages of atypicals, but the few long-term relapse studies comparing a typical antipsychotic to an atypical required time frames of 1 year or longer to show significant differences.[3,4]

EFFICACY

In the CATIE trial, one of the primary explanations for treatment discontinuation that the study examined was a clinical determination of inadequate therapeutic effect, or efficacy failure.[1] During phase 1, time to discontinuation for any cause, including lack of efficacy, was longer for olanzapine than for any other treatment, and more of the patients receiving olanzapine remained on their medication for the duration of the trial than those receiving any of the other study medications (Figure 1).[5] Although olanzapine showed the greatest initial improvement, this advantage diminished over time. Notably, the efficacy results for the atypicals did not differ greatly from those for perphenazine, and none of the treatments under investigation showed exceptional performance. At 18 months, only 36%

Figure 2. Percentage of Subjects Who Discontinued Treatment in CATIE Phase 2E[a]



[a]Data from McEvoy et al.[7]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Table 1. Changes in QLS Scores During CUtLASS 1[a,b]

	FGA Arm		SGA Arm	
Assessment Point	Patients, No.	QLS Total Score, Mean (SD)	Patients, No.	QLS Total Score, Mean (SD)
Baseline	118	43.3 (21.7)	108	43.5 (20.3)
12 wk	100	49.2 (19.9)	87	46.6 (19.0)
26 wk	93	49.2 (20.5)	87	50.4 (18.8)
52 wk	100	53.2 (21.2)	85	51.3 (19.6)

[a]Reprinted with permission from Jones et al.[2]
[b]Values for occasional missing items were imputed using the median of observed responses within other subscales for that patient. Higher scores mean higher quality of life.
Abbreviations: CUtLASS 1 = Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, FGA = first-generation antipsychotic, QLS = Quality of Life Scale, SGA = second-generation antipsychotic.

of patients were still taking olanzapine, compared with 18% to 26% still taking the other drugs.[5] The PANSS scores for phase 1 showed that most of the participants in CATIE experienced improvement, but no significant difference was found between perphenazine and the atypical antipsychotic drugs.[6]

In phase 2 of CATIE, those individuals who had discontinued their medication in phase 1 for lack of efficacy entered the efficacy arm, or phase 2E, in which participants were randomly assigned to open-label treatment with clozapine or blinded treatment with olanzapine, quetiapine, or risperidone (but not the agent they had taken in phase 1).[7] Clozapine was used in this phase because it has been found to be a highly effective antipsychotic that is superior to other antipsychotics for treatment of refractory patients. Despite its proven efficacy, the use of clozapine has been limited due to its potential to induce serious side effects, and its open-label status in CATIE was required because of the need for blood testing. In phase 2, significantly fewer patients taking clozapine discontinued treatment for lack of efficacy than those taking olanzapine ($p < .02$), quetiapine ($p = .004$), or risperidone ($p = .003$).[7] Time to discontinuation for lack of efficacy was longer with clozapine than the other drugs, and more clozapine-treated patients continued taking their medication for the duration of the trial than those taking the other medications (Figure 2). Time to discontinuation due to intolerable side effects did not differ significantly between treatments. Thus, clozapine was found to be superior to all other treatments for people who had experienced inadequate treatment response to antipsychotic exposure in phase 1.

The efficacy results of the CUtLASS 1 study[2] were similar to those of CATIE phase 1. Although the investigators had hypothesized that atypical antipsychotics would be associated with a significant improvement in quality of life, they did not find evidence to support this hypothesis. In fact, the conventional antipsychotics were associated with a slightly greater improvement on the QLS than atypical antipsychotics at 12 weeks and at 52 weeks, but differences were not statistically significant (Table 1).[2] Forty-nine percent of those who received conventional antipsychotics experienced clinically significant improvement on the QLS, compared with 33% of those who received atypical antipsychotics.[8] The results of improvements on the PANSS total score also slightly favored the conventional drugs, with 24% of those receiving conventional drugs experiencing clinically significant improvement versus 18% of those receiving an atypical agent.

Taken together, the efficacy results of the CATIE and CUtLASS 1 trials appear to contradict existing treatment guidelines[9] that advocate the use of atypical antipsychotics as first-line treatment for schizophrenia. However, in addition to being efficacious, drugs must be safe and tolerable in order for them to be viable treatment options. The CATIE and CUtLASS 1 trials provided not only efficacy but also safety and tolerability comparisons.

SAFETY AND TOLERABILITY

Drug safety is particularly important in individuals with severe mental illness such as schizophrenia because this population is often already in poor health. In the United States, the lifespan of individuals with severe mental illness is 13 to more than 30 years shorter than those without mental illness.[10,11] Although suicide is responsible for some of these premature deaths, the majority of individuals with severe mental illness die of natural causes, with the leading cause of death being heart disease. Excess mortality in this population is also seen from cancer and cerebrovascular, respiratory, and pulmonary disease.[11] A great deal of the excess mortality from cardiovascular disease among individuals with schizophrenia is attributable to the prevalence of modifiable risk factors such as smoking, obesity, and diabetes in this population.[10,12] Further-

Table 2. Summary of Side Effects With Commonly Used Antipsychotics[a]

Medication	Extrapyramidal Side Effects/ Tardive Dyskinesia	Prolactin Elevation	Weight Gain	Glucose Abnormalities	Lipid Abnormalities	Sedation	Hypotension	Anticholinergic Side Effects
Perphenazine	++	++	+	+?	+?	+	+	0
Haloperidol	+++	+++	+	0	0	++	0	0
Clozapine	0	0	+++	+++	+++	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	0
Olanzapine	0	0	+++	+++	+++	+	+	++
Quetiapine	0	0	++	++	++	++	++	0
Ziprasidone	0	+	0	0	0	0	0	0
Aripiprazole	0	0	0	0	0	+	0	0

[a]Adapted with permission from the American Psychiatric Association *Practice Guideline for the Treatment of Patients With Schizophrenia*, second edition.[9]
Symbols: 0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose, ++ = sometimes causes side effects at therapeutic dose, +++ = frequently causes side effects at therapeutic dose, ? = data too limited to rate with confidence.

Table 3. Change From Baseline in Metabolic Outcomes in CATIE Phase 1[a,b]

Measure	Olanzapine (mean ± SE)	Quetiapine (mean ± SE)	Risperidone (mean ± SE)	Perphenazine (mean ± SE)	Ziprasidone (mean ± SE)
Weight (lb/mo)	2.0 ± 0.3	0.5 ± 0.2	0.4 ± 0.3	–0.2 ± 0.2	–0.3 ± 0.3
Blood glucose (mg/dL)	13.7 ± 2.5	7.5 ± 2.5	6.6 ± 2.5	5.4 ± 2.8	2.9 ± 3.4
Hemoglobin A1C (%)	0.40 ± 0.07	0.04 ± 0.08	0.07 ± 0.08	0.09 ± 0.09	0.11 ± 0.09
Cholesterol (mg/dL)	9.4 ± 2.4	6.6 ± 2.4	–1.3 ± 2.4	1.5 ± 2.7	–8.2 ± 3.2
Triglycerides (mg/dL)	40.5 ±8.9	21.2 ± 9.2	–2.4 ± 9.1	9.2 ± 10.1	–16.5 ± 12.2

[a]Data from Lieberman et al.[5]
[b]All means are exposure adjusted, except for weight data presented as lb/mo.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

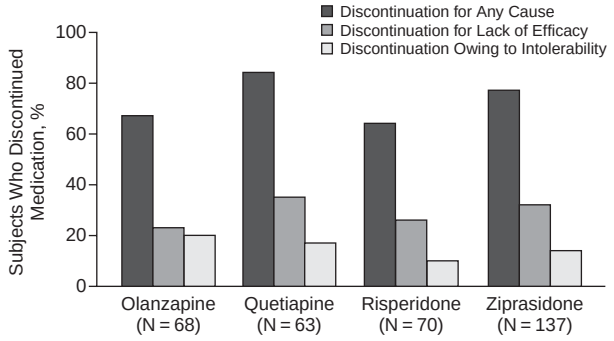
more, the increased mortality among individuals with schizophrenia is exacerbated by the inadequate health care that this population typically receives. Data from the CATIE trial revealed low rates of treatment for common medical disorders such as hypertension, dyslipidemia, and diabetes among individuals entering phase 1.[13]

Because individuals with schizophrenia have many risk factors that may predispose them to poor health and excess mortality, safety of antipsychotic medications is an important treatment concern. Safety concerns have shifted in recent years as the use of atypical antipsychotics has increased and largely replaced the older, conventional drugs. Fifteen to 20 years ago, the primary concerns with antipsychotic treatment were movement disorders such as tardive dyskinesia, as well as sedation, orthostasis, and rare occurrences of QTc prolongation.[14] Currently, the major concerns related to atypical antipsychotic treatment are metabolic disturbances such as diabetes, weight gain, hyperlipidemia, and the resultant increased risk for coronary artery disease. The side effect profiles of antipsychotic medications, both conventional and atypical, vary considerably (Table 2),[9] with certain medications having higher metabolic liabilities (e.g., clozapine, olanzapine), and agents with high affinity for postsynaptic dopamine receptors having greater likelihood for movement disorders (e.g., haloperidol).

The CATIE and CUtLASS trials both examined tolerability and safety as important secondary outcome measures, since both contribute to long-term quality of life and adherence with medications. In the CUtLASS 1 study,[2] patients in both the conventional and atypical arms experienced improvement on most of the side effect variables measured. The only variable in which those on conventional drugs did not experience better outcomes was tardive dyskinesia ratings, using the Abnormal Involuntary Movement Scale.[2] In the CATIE trial,[5] tolerability was assessed as one of the potential reasons for treatment discontinuation. During phase 1, the investigators found no significant differences between those taking the conventional drug perphenazine and those taking an atypical drug in terms of discontinuation due to intolerable side effects, with risperidone having the lowest rate overall of discontinuation due to intolerable side effects (see Figure 1).[5] In terms of specific side effects, no significant differences in incidence of extrapyramidal side effects, akathisia, or movement disorders were found between the groups. More weight gain and metabolic changes were observed in the atypical group but varied by drug (Table 3). For example, weight gain and additional adverse effects associated with the development of metabolic syndrome were most common in the olanzapine group, but ziprasidone was associated with improvement in these metabolic variables.

CATIE subjects who discontinued treatment in phase 1 due to intolerable side effects entered the tolerability arm of phase 2, or phase 2T.[15] Patients who did not wish to be

Figure 3. Percentage of Subjects Who Discontinued Treatment in CATIE Phase 2T[a]



[a]Data from Stroup et al.[15]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

assigned to clozapine and those who had discontinued their phase 1 treatment independently of their doctor's recommendation also entered phase 2T. In this phase, patients were randomly assigned to receive olanzapine, quetiapine, risperidone, or ziprasidone (but not the drug they had previously received in phase 1). In phase 2T, discontinuation of treatment for any cause was least with risperidone and olanzapine, and discontinuation for lack of tolerability was least with risperidone and ziprasidone (Figure 3). No significant differences in the incidence of neurologic side effects, such as extrapyramidal symptoms or akathisia, were observed between treatment groups. As in phase 1, metabolic side effects differed between drugs (Table 4). The olanzapine group experienced the greatest weight gain, the ziprasidone group experienced weight loss, and the patients receiving risperidone or quetiapine did not experience any significant changes in body weight. For total cholesterol and triglycerides, the olanzapine group experienced the greatest increases while the risperidone and ziprasidone groups experienced decreases. As seen in phase 1, the majority of patients (74%) also discontinued treatment in phase 2, and the median duration of treatment was only 4 months.

STUDY LIMITATIONS

The CATIE[1] and CUtLASS 1[2] studies were important trials that added significant new perspectives on antipsychotic safety and efficacy, but they had some limitations. One issue in the CATIE study is antipsychotic dosing. Olanzapine was used at a dose that was slightly higher than that generally used in the community, and ziprasidone was used at a dose that was slightly below average; these variables may have affected psychiatric outcomes.[5,15] A limitation of the CUtLASS 1 study may have been the small sample size. The sample consisted of 118 patients in the conventional arm and 109 patients in the atypical arm, but this sample size may not have been large enough to have the statistical power to show some of the differences between the conventional and atypical drugs. Another limitation of both studies is that the duration of exposure might not have been long enough for the differences between treatment groups to emerge. For example, the average duration of exposure to perphenazine in CATIE was 6 months.[5] Given the fact that patients will ideally stay on their medication for years, the data from these studies need to be used with caution.

A meta-analysis conducted by Leucht and colleagues[16] illustrated the importance of adequate statistical power. This meta-analysis examined a number of randomized controlled trials in which atypical antipsychotics were compared with either conventional antipsychotics or placebo for maintenance treatment of schizophrenia. The duration of exposure for trials to be included was a minimum of 6 months. Although no statistically significant difference was found between the conventional and atypical antipsychotics when the studies were examined individually, the atypical antipsychotics did emerge as more effective against relapse and treatment failure than the older drugs when the data were pooled. Thus, the greater statistical power of the pooled analysis was able to show that the atypical antipsychotics as a group were significantly superior to the conventional drugs (95% CI = 8 to 25). Furthermore, the 3 trials of longest duration found an increasing superiority of the new drugs over time.

One of the studies[3] included in the meta-analysis by Leucht et al.[16] compared risperidone with haloperidol for prevention of relapse in schizophrenia over 2 years. Compliance in both treatment groups was high (97% for risperidone and 96% for haloperidol). Risperidone treatment was associated with a significantly reduced risk of relapse (95% CI = 25 to 64) compared with haloperidol, as well as greater efficacy and tolerability.[3] However, the benefits of treatment with risperidone did not become significant until after several months of treatment. A more recent study[4] compared ziprasidone with haloperidol for treatment of schizophrenia over 3 years and found that ziprasidone was associated with higher rates of remission and greater improvements in quality of life than haloperidol. Similar to the risperidone study, this study did not detect substantial differences between ziprasidone and haloperidol until after 40 weeks of treatment. Both of these studies underscore that differences between the typical and atypical antipsychotics may become apparent over time.

MONITORING

Although the atypical antipsychotics may emerge as more effective treatments than conventional agents for the long-term prevention of relapse in schizophrenia, atypical antipsychotics are not without safety problems. The psy-

Table 4. Change From Baseline in Metabolic Outcomes in CATIE Phase 2T[a,b]

Measure	Olanzapine (mean ± SE)	Quetiapine (mean ± SE)	Risperidone (mean ± SE)	Ziprasidone (mean ± SE)
Weight (lb/mo)	1.3 ± 0.6	0.1 ± 0.6	–0.2 ± 0.4	–1.7 ± 0.5
Blood glucose (mg/dL)	13.8 ± 5.9	1.2 ± 6.0	6.9 ± 5.8	0.8 ± 5.6
Hemoglobin A1C (%)	0.97 ± 0.30	0.61 ± 0.30	0.49 ± 0.30	0.46 ± 0.30
Cholesterol (mg/dL)	17.5 ± 5.2	6.5 ± 5.3	–3.1 ± 5.2	–10.7 ± 5.1
Triglycerides (mg/dL)	94.1 ± 21.8	39.3 ± 22.1	–5.2 ± 21.6	–3.5 ± 20.9

[a]Data from Stroup et al.[15]
[b]All means are exposure adjusted, except for weight data presented as lb/mo.
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

chiatric community has come to recognize that monitoring of metabolic side effects is the standard of care for patients treated with antipsychotics. All patients need to have baseline measurements taken of weight, blood pressure, glucose, and lipids, and these measures need to be monitored throughout treatment.[17] When patients experience metabolic side effects, one option is switching the patient to a different atypical antipsychotic. A study by Casey et al.[18] found that when patients who had been receiving treatment with olanzapine, risperidone, or haloperidol were switched to aripiprazole, they lost between 2.9 lb (1.3 kg) and 3.8 lb (1.7 kg) of body weight after 8 weeks of the new treatment. Another switch study by Weiden and colleagues[19] examined patients who were switched from olanzapine or risperidone to ziprasidone. After 1 year of ziprasidone treatment, those patients who had been switched from olanzapine lost an average of 9.4 lb (4.2 kg) and those who had been switched from risperidone lost an average of 11.3 lb (5.1 kg). Additionally, both of these groups of patients experienced improvements in body mass index and triglyceride and cholesterol levels.

CONCLUSION

In summary, treatment options for patients with schizophrenia are far more plentiful than they were 15 to 20 years ago. The newer antipsychotics appear to be slightly more effective than the older agents, but finding evidence to support that belief has been difficult. Studies with longer duration and adequate statistical power are needed to answer this question. Like the older agents, the atypical antipsychotics also present some safety and tolerability concerns. Because individuals with schizophrenia experience high rates of health problems and excess mortality, clinicians must strive to forestall negative outcomes not only by factoring safety and efficacy considerations into the selection of antipsychotic treatment, but also by adequately monitoring patients' health and addressing these issues as they arise.

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 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.

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