

Putting Metabolic Side Effects Into Perspective: Risks Versus Benefits of Atypical Antipsychotics

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© The lengthy list of the side effects and morbidity associated with the atypical antipsychotics might make a patient with psychosis and his or her caregivers so concerned about the use of any of these medications, particularly those associated with a higher risk of diabetes, weight gain, or increased lipid levels, that they would prefer to avoid all of them. However, schizophrenia is associated with a relatively high risk for several diseases, including diabetes, that is independent of the risks that are linked to atypical antipsychotic use. Therefore, the clinician who might think, “Why use atypicals if using the typical drugs will escape the problems of monitoring and all the associated effects of diabetes and hyperglycemia?” needs to know that these problems cannot be avoided simply by choosing typical antipsychotics. Clinicians, patients, and concerned family members must balance the significant benefits of atypical antipsychotic treatment—improved cognition, reduced suicidality, and less depression—against the risks of metabolic disturbances and select a course of treatment that includes a realistic monitoring program.

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The lengthy list of the metabolic side effects and morbidity associated with the atypical antipsychotics might make a patient with psychosis and his or her caregivers so concerned about the use of any of these medications, particularly those associated with a higher risk of diabetes, weight gain, or increased lipid levels, that they would prefer to avoid all of them. However, clinicians, patients, and concerned family members must balance the significant benefits of atypical antipsychotic treatment—improved cognition, less depression, and reduced suicidality—against the risks of metabolic disturbances and select a course of treatment that includes a realistic monitoring program.

Schizophrenia is associated with a relatively high risk for several diseases, including diabetes, that is separate from the risk that is linked with atypical antipsychotic use. For example, a recent study by Brown et al.¹ identified a cohort of 370 patients who had had contact with an English psychiatric service in 1981; these patients were followed up at the end of 1994. Of note, most of the atypical antipsychotics were introduced after this study ended, and none were in common use in England during the time

of the study. The overall mortality rate with schizophrenia (using the standardized mortality ratio) was about 3 times higher than that expected in the general population, adjusting for age and gender. Much of this difference was due to the increased rate of suicide, which was 28 times that of the general population. However, an increased rate of death due to natural causes, including diabetes, was also found in the study group. Death due to diabetes was almost 10 times that in the normal control population, and it ranked as the third leading cause of death among patients with schizophrenia behind suicide and epilepsy. Therefore, the clinician who might think, “Why use atypicals if using the typical drugs will escape the problems of monitoring and all the associated effects of diabetes and hyperglycemia?” would not avoid these problems by avoiding the atypical antipsychotics.

COMPLIANCE

The typical neuroleptics have a number of serious limitations in efficacy compared with the atypical drugs, and the noncompliance rate with the typical drugs is much higher than that associated with the atypical drugs. Although compliance can be measured in many ways, Wright² has reported that only about one third of patients are compliant with medication, another third are partially compliant, and the last third are noncompliant. The overall compliance rate, therefore, is around 50%.² Intolerable side effects, especially extrapyramidal symptoms (EPS) such as tardive dyskinesia, are typically implicated when patients decide to stop taking their typical antipsychotic medication. Murray and van Os³ concluded in their review of predic-

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tors of outcome that the presence of EPS is a strong predictor of patient noncompliance and, therefore, poor outcome. Oehl et al.⁴ also cite EPS as a common reason for noncompliance. The reduced rate of EPS and tardive dyskinesia with all the atypical antipsychotics⁵ is, therefore, a tremendous advantage that can only have a positive impact on compliance.

Besides EPS, another oft-cited reason for noncompliance with antipsychotic treatment is weight gain. Weiden et al.⁶ found a significant association between weight and noncompliance. An 8-page questionnaire was sent to individuals with schizophrenia, and obese respondents were much more likely to report skipping medication doses. This group was also more likely to discontinue medication treatment because of weight gain. Unlike EPS, weight gain, at times significant amounts, is seen with both typical and atypical antipsychotics, although some drugs seem to be more liable to cause it than others. Allison and colleagues⁷ reported that, among atypical antipsychotics, sertindole, risperidone, and ziprasidone were associated with less weight gain than were clozapine and olanzapine. Wirshing and coworkers⁸ found similar results in their retrospective chart review of male patients with schizophrenia. Clozapine and olanzapine were associated with more weight gain in that study than either risperidone or sertindole.

QUALITY OF LIFE

Schizophrenia is a serious disease, independent of the medical issues that can make it difficult to treat. The quality of life associated with schizophrenia ranks among the worst of any chronic medical illness. In the average schizophrenic patient, the atypical antipsychotics as a group—risperidone, olanzapine, quetiapine, and clozapine—have significant advantages over the typicals for treating positive and negative symptoms. The greatest advantage of these drugs, which is in most cases worth the risk of metabolic changes, is their ability to improve cognition, now considered to be the fundamental feature of schizophrenia. Improved cognition can lead to improved functioning in both home and work environments. In addition, the atypical antipsychotics have been shown to decrease depression in patients with schizophrenia. Clozapine has been found to reduce suicidality.⁹

Cognition

The atypical antipsychotics have been shown to significantly improve many aspects of cognitive function,¹⁰ including executive function, verbal fluency, attention, and memory and learning.¹¹ Executive function encompasses a variety of problem-solving and reasoning skills. In a study of risperidone and clozapine versus typical antipsychotics, the patients treated with the atypical agents performed better on maze tests than those treated with the typical drugs.¹² Clozapine-treated patients were able to solve mazes more

quickly, but risperidone-treated patients made fewer errors. Other studies have also found that the atypical antipsychotics improve this type of problem-solving ability. A study of clozapine and zotepine¹³ in schizophrenic patients found that participants in both medication groups experienced an improvement in maze test results, but zotepine-treated patients saw more improvement. Gallhofer et al.¹⁴ found similar results on maze tests in both risperidone- and clozapine-treated patients. Risperidone has also been reported to improve executive function as measured by a card sorting test.¹⁵ Recent literature reviews^{16,17} of atypical antipsychotics and cognition confirmed that clozapine, risperidone, and olanzapine all have a positive impact on executive function.

Verbal fluency and attention are other important areas of cognitive function that are often impaired in people with schizophrenia. The inability to form sentences or find words severely hampers social interactions, in both work and interpersonal relationships, as does the inability to focus and concentrate on the task or person at hand. Again, the atypical antipsychotics have been shown to improve verbal fluency and attention in schizophrenic patients. Meltzer and McGurk¹⁶ found in their literature review that clozapine and olanzapine have an especially positive impact on verbal fluency, whereas clozapine and risperidone have a beneficial effect on attention. Other studies^{18,19} have found similar results for clozapine and its impact on both verbal fluency and attention, and Stip and Lussier²⁰ confirmed the positive effect of risperidone on attention.

Problems with memory and learning, another common cognitive deficit in schizophrenia, can also have a detrimental impact on a schizophrenic patient's attempts to gain employment or succeed in school. Green et al.²¹ studied the impact of risperidone or haloperidol on verbal working memory in treatment-resistant schizophrenic patients. After 4 weeks of double-blind treatment, risperidone-treated patients saw more improvement in verbal working memory than did the haloperidol-treated patients. Meltzer and McGurk¹⁶ found in their literature review that risperidone consistently improved working memory, whereas olanzapine had a favorable effect on verbal memory. Another review¹⁹ also concluded that risperidone ameliorates problems with working memory in patients with schizophrenia.

The beneficial effects of the atypical antipsychotics on cognition are an important determinant of work and social function. A recent study²² found a clear association between unemployment and cognitive dysfunction in schizophrenic patients. Those patients who were able to work full time performed better on several measures of cognition, such as vigilance, executive functioning, and working memory.

Cognitive function can serve as a reliable predictor of outcome in schizophrenia. Stip et al.²³ found verbal fluency to be a reliable and sensitive predictor of response to atypical antipsychotic treatment. Those patients who performed well on tests of verbal fluency were more likely to

be responders as measured by the Positive and Negative Syndrome Scale. Control of positive symptoms, through the strength of the typical drugs, does not necessarily have an impact on cognition. In fact, the typical neuroleptics have been shown to impair cognitive function.^{24,25}

Depression and Suicide

Another critical factor in quality of life in schizophrenia is depression. Patients with schizophrenia who feel their illness is beyond their control are more likely to be depressed than those who feel more in control, implying that depression can be a psychological response to psychosis.²⁶ Roy et al.²⁷ discovered that depressed schizophrenic patients were hospitalized more often, had more history of depression, had attempted suicide more often, were more likely to live alone, and were more likely to have low self-esteem than schizophrenic patients who were not depressed. Clearly, if a clinician wants to better the quality of life of a depressed psychotic patient, he or she must treat the depression along with the psychosis.

The atypical antipsychotics have been shown to be effective in treating depression both as monotherapy and adjunct to antidepressant therapy. For example, Nacasch and colleagues²⁸ report 3 cases in which clozapine was used to treat patients who had major depressive disorder with agitation. All 3 responded well to clozapine treatment. Clozapine was also a successful treatment in 3 cases of treatment-resistant psychotic depression.²⁹ Hillert and co-workers³⁰ report a case series of 10 patients with psychotic depression who were treated with risperidone. Psychosis decreased in all 10; depression decreased in 7 patients. Another case series³¹ of 4 patients with chronic depression found that the combination of risperidone and a selective serotonin reuptake inhibitor was effective in alleviating depressive symptoms.

The combination of schizophrenia and depression can also be treated with atypical antipsychotics. In a double-blind, parallel-group study,³² 29 patients were started on fluphenazine treatment, then switched to either clozapine or risperidone. Both groups saw similar improvement on depression scores; however, improvement with clozapine was significant compared with the baseline fluphenazine-treatment scores. Tollefson and colleagues³³ compared the effects of olanzapine versus those of haloperidol or placebo on anxiety and depression in schizophrenic patients. They found that olanzapine, 10 ± 2.5 and 15 ± 2.5 mg/day, was significantly superior to placebo in improving anxiety and depression, a difference not seen with haloperidol treatment. In a different study, Tollefson and colleagues³⁴ found similar results. Olanzapine-treated schizophrenic patients experienced a significant improvement in Montgomery-Asberg Depression Rating Scale score compared with the haloperidol-treated patients. The response rate in the olanzapine group was also significantly higher than that in the haloperidol group.

Although the rate of depression in schizophrenia has yet to be quantified, the suicide rate among those with schizophrenia has been. Caldwell and Gottesman³⁵ report that 10% to 13% of people with schizophrenia commit suicide, with young white men at highest risk. In their study of the excess mortality of schizophrenia, Brown et al.¹ found that the rate of unnatural death was 12 times that expected in the general population. This category included clear cases of suicide as well as accidents and death due to undetermined causes, which probably included some suicides as well. In an earlier meta-analysis of excess mortality in schizophrenia, Brown³⁶ found that 12% of reported deaths were suicides, and that suicide accounted for 28% of the excess mortality, the largest contributor among all causes of death. The suicide rate among all studies analyzed was 8 times that seen in the general population.

The clinician who treats schizophrenia, therefore, must be watchful for signs of suicidality and treat them promptly and effectively if they arise. Some of these signs include depression, especially hopelessness, poor social function, severe illness with frequent relapses and hospitalization, substance abuse, and previous suicide attempts.⁹ My colleague and I⁹ studied the effect of clozapine on suicidality, which includes suicidal thoughts, plans to commit suicide, attempted suicide, and completed suicide, in patients with schizophrenia or schizoaffective disorder. Of the initial study group, which included treatment-responsive as well as treatment-resistant patients, 88 treatment-resistant patients took clozapine for at least 6 months. Among this group, the percentage of patients with no suicidal thoughts increased from 53% to 87%, and the rate of attempted suicide decreased by 86%. Only 3 patients attempted suicide during clozapine treatment, and all 3 admitted that they had no real wish to die. These results were confirmed in a large-scale epidemiologic study,³⁷ which reported that fewer patients on clozapine treatment committed suicide compared with patients who were no longer taking the drug. Overall mortality was also lower during clozapine treatment than during times without clozapine treatment.

In addition, clozapine seems to be more effective than the typical antipsychotics in reducing suicidality. Spivak and others³⁸ compared aggression, impulsiveness, and suicidality in patients with chronic schizophrenia on treatment with either clozapine ($N = 30$) or a typical neuroleptic ($N = 30$) for 1 year. At the end of the study period, patients taking clozapine exhibited significantly less aggression and impulsiveness and fewer suicide attempts.

With clozapine, the risk of dying from agranulocytosis is minimal; according to the most recent prescribing information,³⁹ the risk of death is 1 in 10,000. The risk of dying from suicide for a treatment-resistant schizophrenic is 1 in 10.³⁴ That is an enormous difference in risk, but clinicians seem to be hesitant to prescribe clozapine out of fear of being responsible for the development of agranulocytosis in their patients.

CONCLUSION: FACTORS TO CONSIDER WHEN PRESCRIBING ATYPICAL ANTIPSYCHOTICS

My colleagues and I have completed a study of weight gain with clozapine.⁴⁰ Our results confirm those of Leadbetter and coworkers⁴¹ and others^{42–44} that weight gain associated with clozapine predicts clinical response. Other studies of weight gain with clozapine that had different results tended not to take into account baseline levels of psychopathology, they dichotomized responders and non-responders, or the period of time was insufficient for assessing weight gain. It seems that the patients who gain weight while on atypical antipsychotic therapy may be the very patients who benefit most from these drugs.^{45,46} The findings by Henderson and others⁴⁷ that a third of patients on long-term clozapine treatment have developed diabetes at 5-year follow-up may be related to the fact that the patients who stay on clozapine treatment the longest—the ones who are treated for 5 years—are the patients who have had the best improvement in psychopathology and social and work function. Of course, this type of patient should keep taking the drug, and the clinician and patient should do everything possible to control weight gain, such as increasing activity, decreasing caloric intake, and changing the type of diet.

The atypical antipsychotics have taken over the U.S. marketplace justifiably; they are an enormous advance over the typical neuroleptics. Because these drugs are so effective, even for formerly treatment-resistant patients, clinicians need to find ways to make them safe to use until superior agents are discovered. The clinician, patient, and patient's family have to balance the significant benefits that may come from taking an atypical antipsychotic against the risks of detrimental metabolic changes discussed elsewhere in this supplement. Unfortunately, if these risks are presented in a categorical, unqualified fashion, many clinicians will back away from using the atypical drugs, in the same way they have backed away from using clozapine out of a misunderstanding of the true risk of agranulocytosis. One way for the clinician and patient to cope with the risks is to develop a realistic monitoring program that will detect emerging metabolic disturbances.

Although it is possible to simplify the monitoring process for the clinician and to treat diabetes successfully, it is incumbent upon the treating clinician to ensure patient compliance with the treatment and avoid the development of diabetes if at all possible. The best ways are educating patients in nutrition and diet, prescribing the lowest effective dose, and avoiding ancillary medications which may exacerbate the problem, including mood stabilizers (e.g., valproate). Clinicians also need to take a thorough medical history of their patients, including a family history, measures of weight and height, and a measure of adiposity, and track these over time.

More data are needed that confirm the differences among the atypical antipsychotics to develop a basis for the ratio-

nal choice and switching of drugs. It is also necessary to confirm whether or not there exists a point in antipsychotic drug treatment after which the risk of developing diabetes or gaining weight diminishes significantly. The monitoring process clearly should be very intensive at the early stages. However, if monitoring is conducted every 3 months indefinitely, this level of intensity may turn out to be a significant factor in diminishing the use of these agents.

For psychiatrists, it is also important to build a close working relationship with the internist or the family practice doctor with an interest in diabetes. One of the challenges patients with schizophrenia face is that their overall medical treatment is not what it should be. If, through an increased awareness of possible metabolic changes during atypical antipsychotic treatment, the psychiatric clinician begins to be more alert to the need to assess the overall medical needs of his or her patients during the initial evaluation and then periodically during the course of treatment, then the cloud of these metabolic risks carries with it a silver lining.

Drug names: clozapine (Clozaril 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 has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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