Assessing Cardiovascular Risks Versus Clinical Benefits of Atypical Antipsychotic Drug Treatment

Herbert Y. Meltzer, M.D.; Michael Davidson, M.D.; Alexander H. Glassman, M.D.; and W. Victor R. Vieweg, M.D.

The atypical antipsychotic drugs are a major advance in the treatment of psychosis in spite of concerns about metabolic and cardiovascular side effects that affect morbidity and mortality. Concerns about weight gain, hypoglycemia, diabetes, and increases in lipids as well as sudden death due to torsades de pointes and other cardiovascular events can temper enthusiasm about the atypical antipsychotics. The challenge for the clinician is to weigh the benefits and risks for each drug for each patient and develop a treatment plan with the individual patient in mind. This article discusses both risks and benefits of antipsychotic treatment and presents a treatment algorithm to aid the clinician in choosing medications for the psychotic patient. *(J Clin Psychiatry 2002;63[suppl 9]:25–29)*

In spite of concerns about their metabolic and cardiovascular side effects that affect morbidity and mortality, the atypical antipsychotic drugs represent a major advance in the treatment of schizophrenia, bipolar disorder, psychotic depression, and senile psychoses, among other indications. However, concerns about the ability of the atypical antipsychotic drugs to cause weight gain, hypoglycemia, diabetes, and increases in lipids, as well as sudden death due to torsades de pointes and other cardiovascular events, have produced concern about their extensive use. Clinicians weigh the benefits and risks for these drugs as a class and individually for each patient that they treat and develop a treatment plan with the individual patient in mind. This article discusses both risks and benefits of antipsychotic treatment and presents a treatment algorithm that will hopefully help the clinician in choosing medications for the psychotic patient.

From the Department of Psychiatry and Pharmacology, Division of Psychopharmacology, Vanderbilt University Medical Center, Nashville, Tenn. (Dr. Meltzer); the Department of Psychiatry, Tel Aviv University, Tel Aviv, Israel (Dr. Davidson); the Department of Psychiatry, Columbia University, New York, N.Y. (Dr. Glassman); and the Department of Psychiatry, Medical College of Virginia, Virginia Commonwealth University, Richmond (Dr. Vieweg).

Presented at the teleconference "Cardiovascular and Metabolic Risks Associated With Schizophrenia and Antipsychotic Drug Treatment," which was held August 13, 2001, and supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.

Corresponding author and reprints: Herbert Y. Meltzer, M.D., Department of Psychiatry and Pharmacology, Division of Psychopharmacology, Vanderbilt University Medical Center, 1601 23rd Ave. South, Suite 306, Nashville, TN 37212.

CARDIOVASCULAR SIDE EFFECTS

Historically, only cardiac drugs were thought to have cardiovascular adverse effects. In the last 10 to 15 years, other types of drugs have been found to have these side effects as well. An early instance of a noncardiac drug receiving a "black box" warning in its product information, the strongest warning issued by the U.S. Food and Drug Administration (FDA), was in 1992, when the FDA added the warning to the antihistamine terfenadine. In 1990, that drug was reported to have caused torsades de pointes, an abnormality that is often preceded by QT prolongation and can lead to fatal ventricular arrhythmia.[1] Although terfenadine was not associated with cardiovascular side effects in premarketing studies, those studies, like most, neglected to examine the side effects of terfenadine when taken in conjunction with other drugs. The reality is that most patients take more than one drug at a time, and the 1990 report concluded that torsades de pointes was induced by the combination of terfenadine and ketoconazole. The latter, by inhibiting the metabolism of terfenadine, produced a large increase in plasma terfenadine levels, which, in turn, greatly increased QTc interval and precipitated fatal torsades de pointes.

Cardiovascular risks associated with clozapine, e.g., tachycardia, hypotension, hypertension, and cardiomyopathy, have been known for nearly a decade and are factored into its risk:benefit ratio. Recently, the FDA has revised the package insert for clozapine to indicate increased risk of myocarditis. Clozapine is not known to be associated with prolonged QTc. Sertindole, another atypical antipsychotic, is associated with marked increase in QTc. After its approval in Europe in 1996, a number of sudden deaths

were ascribed to the administration of this drug. Sertindole was withdrawn from use in Europe, and clinical trials in the United States were suspended. However, reexamination of epidemiologic data on the occurence of sudden death with other antipsychotic drugs led European authorities to reinstate sertindole with a restrictive label. It is unknown at this time whether there are plans to register sertindole in the United States. The experience with sertindole highlights the difficulty of assessing cardiovascular risk with antipsychotic drugs and, in particular, assessing the clinical significance of QTc prolongation.

The concern about the greater ability of ziprasidone to elevate the QT interval, while still present, is diminishing. As of February 2002, approximately 160,000 patients have been administered ziprasidone worldwide with no documented incidence of torsades de pointes or cases of sudden death due to other cardiovascular causes. This early experience is encouraging in that the increases in QT interval of the size produced by ziprasidone in the absence of drug-drug interactions may not preclude general use. Routine determination of the QTc before starting ziprasidone or after starting treatment with it is neither required nor recommended. Ziprasidone has yet to be studied in elderly patients or others with high risk for cardiovascular disease. The FDA has revised the package insert to include a list of 21 drugs that have increased liability to elevate the QT interval. Coprescription of these drugs with ziprasidone is not recommended.

The FDA recently requested that the manufacturer of ziprasidone, a new atypical antipsychotic, compare the effect of that drug on the QT interval with that of other antipsychotics. As comparators, the study used oral formulations of thioridazine, quetiapine, risperidone, olanzapine, and haloperidol.[2,3] A low-risk patient group consisting of 164 relatively young men with corrected QT interval (QTc) values in the normal range completed the study.

A mean change in QTc of 10 ms or more in a study of this kind is usually considered to be noteworthy, and in this study,[2,3] 4 of 6 drugs analyzed had a mean change greater than 10 ms. Thioridazine had the greatest mean change by far, at 35.6 ms. Ziprasidone had the next-highest mean change at 20.3 ms, followed by quetiapine at 14.5 ms, risperidone at 11.6 ms, olanzapine at 6.8 ms, and haloperidol at 4.7 ms.

The findings regarding thioridazine prompted the FDA to add a black box warning to that drug's product information even though it had been on the market for many years. Although the thioridazine results were surprising to many, sudden death associated with the drug has been reported in the literature for almost 40 years.[4–6] In a more recent study of 49 cases of sudden death associated with antipsychotics or antidepressants, Mehtonen and colleagues[7] found that thioridazine was the only antipsychotic drug in 15 of those cases. Thioridazine use, alone or in combination, was reported in 28 of 49 cases.

MORTALITY AND SCHIZOPHRENIA

People with schizophrenia and other psychiatric illnesses are at increased risk for death from a variety of reasons, including cardiovascular and metabolic causes. In other words, there is an underlying diathesis that renders this population at greater risk for cardiovascular events than the general population. These risks, combined with the risks of the drugs themselves and lifestyle choices such as smoking, make the cardiovascular death rate among schizophrenic patients higher than that among the general population.

The prevalence of circulatory disease is also high in schizophrenic patients. Over 10 years, Waddington and coworkers[8] followed 88 inpatients with schizophrenia. In that time period, 39 died; no suicides were reported. The relative risk of death among these patients compared with the general population was 1.33. Causes of death included circulatory disease, malignant disease, respiratory disease, injury and poisoning, and "other causes," with circulatory disease being the most common. Treatment with more than one antipsychotic and the lack of adjunctive anticholinergic therapy were associated with reduced survival.

Although Waddington and colleagues[8] saw no suicides in the cohort they followed, suicide is a major contributor to the higher death rate among patients with schizophrenia. One study[9] reported that 10% to 13% of people with schizophrenia commit suicide. In a meta-analysis of excess mortality in schizophrenia, Brown[10] 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. At the end of 1994, Brown et al.[11] followed up with a cohort of 370 patients with schizophrenia who had had contact with an English psychiatric service in 1981. After adjusting for age and gender, the overall mortality rate among the schizophrenic patients was about 3 times higher than that expected in the general population. The rate of suicide in the schizophrenia group was 28 times that of the general population. However, an increased rate of death due to natural causes, including diabetes, was also found. None of the atypical antipsychotics were in common use in England during the time of the study. Much of the excess mortality of schizophrenia is preventable through either lifestyle modification or better treatment.

BENEFITS OF ATYPICAL ANTIPSYCHOTIC TREATMENT

Schizophrenia is associated with an extremely poor quality of life. A 20-year follow-up[12] of all first-episode patients with schizophrenia diagnosed in 1966 or 1967 in Iceland found that 22% had died in that time period; 9% had committed suicide. Most of the patients had difficulties living

a full and productive life; in 1987, just over half remained unmarried, and a third of those who had married were divorced. Social relationships were impaired in almost all (95%) of the patients. The atypical antipsychotics represent real progress in the treatment of psychosis; not only do they control the positive symptoms of psychosis, but they can also improve the negative symptoms and depression as well as cognition. With proper treatment, one can expect the mortality rate among schizophrenic patients to decrease while the quality of life increases.

Treatment of Depression

Depression in schizophrenia may be a psychological response to psychosis; patients with schizophrenia who feel their illness is beyond their control are more likely to be depressed than those who feel more in control.[13] Depressed schizophrenic patients are hospitalized more often, have more history of depression, have attempted suicide more often, are more likely to live alone, and are more likely to have low self-esteem than schizophrenic patients who are not depressed.[14] If clinicians want to improve the quality of life of a depressed psychotic patient, they must treat the depression along with the psychosis.

The combination of schizophrenia and depression can be treated with atypical antipsychotics. Twenty-nine patients in one study[15] were given fluphenazine and were then switched to either clozapine or risperidone. Both groups saw improvement on depression scores, although only the clozapine group saw statistically significant improvement compared with the fluphenazine baseline scores. In a study of anxiety and depression in schizophrenic patients, Tollefson and colleagues[16] compared the effects of olanzapine versus those of haloperidol or placebo. Olanzapine, but not haloperidol, was significantly superior to placebo in improving anxiety and depression.

Treating depression in schizophrenic patients may decrease the rate of suicide in that population. Depression, especially hopelessness, is a warning sign for suicidality, as are poor social function, severe illness with frequent relapses and hospitalization, substance abuse, and previous suicide attempts. My colleague and I[17] 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. Among a group of 88 treatment-resistant patients who took clozapine for at least 6 months, 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. A large-scale epidemiologic study[18] confirmed these results, reporting 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.

Clozapine provides an excellent lesson in balancing the risks and benefits of treatment. The risk of dying from agranulocytosis due to clozapine treatment is minimal; according to the product information,[19] the risk of death is 1 in 10,000. The risk of dying from suicide for a treatment-resistant schizophrenic is 1 in 10.[20] Despite the substantial difference in risk, clinicians seem to be hesitant to prescribe clozapine out of fear of being responsible for the development of agranulocytosis in their patients even though clozapine may help some patients survive schizophrenia.

Improvement in Cognition

One of the great advantages of the atypical antipsychotics is their ability to improve impaired cognition, which is considered to be the fundamental feature of schizophrenia. Improved cognition can lead to improved functioning in both home and work environments. Control of positive symptoms, 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.[21,22] On the other hand, atypical antipsychotics improve many aspects of cognitive function,[23] including executive function (problem solving and reasoning), verbal fluency, attention, and memory and learning.[24]

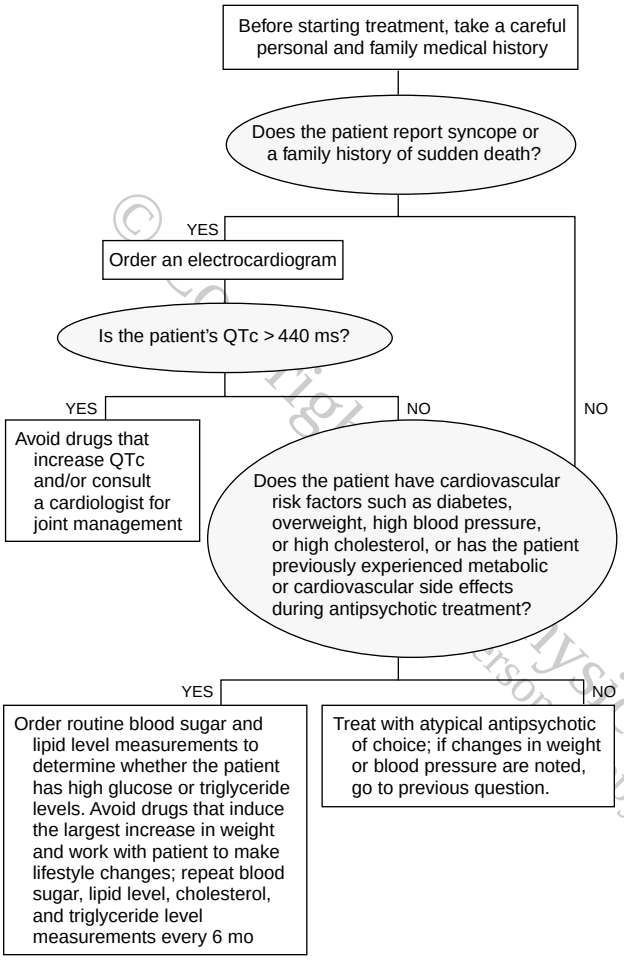
For example, risperidone and clozapine were compared with the typical drugs on maze solving, a measure of executive function.[25] Both atypical antipsychotics were associated with better results. The clozapine-treated patients solved the mazes more quickly, but the risperidone-treated patients made fewer mistakes. Literature reviews[26,27] have found that clozapine, risperidone, and olanzapine are all associated with improvements in executive function. People with schizophrenia are often impaired in verbal fluency and attention as well. Clozapine and olanzapine have a beneficial impact on verbal fluency, whereas clozapine and risperidone have a positive effect on attention.[26–29] In the area of memory, risperidone has been found to consistently improve working memory, and olanzapine, verbal memory.[26]

The beneficial effects of the atypical antipsychotics on cognition are an important determinant of work and social function. In one study, a colleague and I[30] found a clear association between unemployment and cognitive dysfunction in schizophrenic patients. Patients able to work full time performed better on measures of cognition such as vigilance, executive functioning, and working memory. Cognitive function is also a predictor of outcome in schizophrenia,[31] so improving cognitive function is of the highest importance when treating patients with schizophrenia.

TREATMENT ALGORITHM

An algorithm to help the clinician make choices among the atypical antipsychotics is presented in Figure 1. If there is evidence of a long QTc, QTc-prolonging drugs like ziprasidone and thioridazine should be avoided. If a patient has

Figure 1. Treatment Algorithm: Assessing Cardiac and Metabolic Risks in Apparently Healthy Young or Middle-Aged Patients



elevated lipid levels, is obese, or is diabetic, drugs with increased likelihood of causing the greatest weight gain, such as olanzapine and clozapine, are less favored. The frequency of monitoring cardiovascular status in patients who have preexisting risk factors should be at least every 6 months.

Clinical considerations may in some cases override some cardiovascular and metabolic concerns. For example, a clozapine trial in a treatment-resistant patient who has failed 2 or 3 trials of the other atypical antipsychotics should not be rejected on the sole basis that there might be further increase in weight or lipid levels. For that patient, clozapine may be prescribed along with an intense effort to deal with lifestyle issues and perhaps a statin to reduce the patient's cholesterol level. Metabolic side effects are often dose dependent; therefore, it would be important in this and similar situations to keep the dose of any drug with metabolic side effects as low as possible.

CONCLUSION

It is important to remember that the atypical antipsychotics are a remarkable group of drugs. Their lower risk for tardive dyskinesia and extrapyramidal symptoms and their beneficial effects on cognition, mood, and negative symptoms deservedly make them the first line of treatment for psychosis. Psychiatrists have access to internists, cardiologists, and family doctors to help with the management of patients who are at risk and should not refrain from utilizing a drug when the psychiatric condition clearly indicates that the drug can be of value.

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

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

REFERENCES

1. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsades de pointes occurring in association with terfenadine use. JAMA 1990;264:2788–2790
2. FDA Psychopharmacological Drugs Advisory Committee. Briefing Document for Zeldox Capsules (ziprasidone HCl). July 19, 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf and 3619b1b.pdf. Accessed Nov 28, 2001
3. Food and Drug Administration, Center for Drug Evaluation and Research Psychopharmacological Drugs Advisory Committee. Meeting Transcript. July 19, 2000. Available at: http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3619t1a.pdf, 3619t1b.pdf, and 3619t1c.pdf. Accessed Nov 28, 2001
4. Kelly HG, Fay JE, Lavery SG. Thioridazine hydrochloride (Mellaril): its effects on the electrocardiogram and a report of two fatalities with electrocardiographic abnormalities. Can Med Assoc J 1963;89:546–554
5. Giles TD, Modlin RK. Death associated with ventricular arrhythmia and thioridazine hydrochloride. JAMA 1968;205:108–110
6. Goodson WH Jr, Litkenhous EE Jr. Sudden unexplained death in a psychiatric patient taking thioridazine. South Med J 1976;69:311, 315, 320
7. Mehtonen O-P, Aranko K, Malkonen L, et al. A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta Psychiatr Scand 1991;84:58–64
8. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. Br J Psychiatry 1998;173:325–329
9. Caldwell CB, Gottesman II. Schizophrenics kill themselves too: review of risk factors for suicide. Schizophr Bull 1990;16:571–589
10. Brown S. Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997;171:502–508
11. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000;177:212–217
12. Helgason L. Twenty years' follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? Acta Psychiatr Scand 1990;81:231–235
13. Birchwood M, Mason R, MacMillan F, et al. Depression, demoralization and control over psychotic illness: a comparison of depressed and non-depressed patients with chronic psychosis. Psychol Med 1993;23:387–395
14. Roy A, Thompson R, Kennedy S. Depression in chronic schizophrenia. Br J Psychiatry 1983;142:465–470
15. Breier AF, Malhotra AK, Tung-Ping S, et al. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. Am J Psychiatry 1999;156:294–298
16. Tollefson GD, Sanger TM, Beasley CM, et al. Double-blind, controlled

comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998;43:803–810
17. Meltzer HY, Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183–190
18. Walker AM, Lanza LL, Arellano F, et al. Mortality in current and former users of clozapine. Epidemiology 1997;8:671–677
19. Clozaril (clozapine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2001:2155–2159
20. Tollefson GD, Sanger TM, Lu Y, et al. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55:250–258
21. Velligan DI, Miller AL. Cognitive dysfunction in schizophrenia and its importance to outcome: the place of atypical antipsychotics in treatment. J Clin Psychiatry 1999;60(suppl 23):25–28
22. Stip E. Memory impairment in schizophrenia: perspectives from psychopathology and pharmacotherapy. Can J Psychiatry 1996;41(suppl 2): 27S–34S
23. Keefe RS, Silva SG, Perkins DO, et al. Effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 1999;25:201–202
24. Collaborative Working Group on Clinical Trial Evaluations. Evaluating the effects of antipsychotics on cognition in schizophrenia. J Clin Psychiatry 1998;59(suppl 12):35–40
25. Gallhofer B, Lis S, Meyer-Lindenberg A, et al. Cognitive dysfunction in schizophrenia: a new set of tools for the assessment of cognition and drug effects. Acta Psychiatr Scand 1999;99(suppl 395):118–128
26. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 1999;25: 233–255
27. Velligan DI, Bow-Thomas CC. Executive function in schizophrenia. Semin Clin Neuropsychiatry 1999;4:24–33
28. Lee MA, Thompson PA, Meltzer HY. Effects of clozapine on cognitive function in schizophrenia. J Clin Psychiatry 1994;55(9, suppl B):82–87
29. Stip E, Lussier I. Effect of risperidone on cognition in patients with schizophrenia. Can J Psychiatry 1996;41(2, suppl):35S–40S
30. McGurk SR, Meltzer HY. Role of cognition in vocational functioning in schizophrenia. Schizophr Res 2000;45:175–184
31. Stip E, Lussier I, Ngan E, et al. Discriminant cognitive factors in responder and nonresponder patients with schizophrenia. Eur Psychiatry 1999;14: 442–450