Side Effects as Influencers of Treatment Outcome

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Research relative to the efficacy of a therapeutic agent commands a clinician's greatest interest, but treatment decisions are made based on optimizing efficacy and tolerability/safety considerations. Second-generation atypical antipsychotic drugs are a study in the importance of taking a careful look at the full benefit-risk profile of each drug. The disorders that atypical antipsychotics are approved to treat—schizophrenia, schizoaffective disorder, and bipolar disorder—are associated with an increased rate of certain medical comorbidities compared to the general population. Between-drug differences in efficacy are relatively modest for the atypicals, or between atypicals and conventionals, while differences in safety and tolerability are larger and more clinically relevant. The current article will provide a brief summary of safety-related issues that influence treatment outcome and choice of drug.

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PATIENTS WITH BIPOLAR DISORDER AND SCHIZOPHRENIA ARE A POPULATION AT RISK FOR MEDICAL DISORDERS

A growing body of epidemiologic research indicates that affectively ill individuals have increased mortality rates from both suicide and other medical causes. For example, one large population sample[1] found the standardized mortality ratio (SMR) versus the general population for all causes to be significantly higher for both unipolar depression (male = 2.0, female = 2.0) and bipolar disorder (male = 2.5, female = 2.7). The SMR for suicide was high for both unipolar depression (male = 20.9, female = 27.0) and bipolar disorder (male = 15.0, female = 22.4). These SMRs are similar to what has been reported in other population-based samples.[2]

Notable in this study was the increased SMR attributable to natural causes for both unipolar depression (male = 1.5, female = 1.6) and bipolar disorder (male = 1.9, female = 2.1). Natural causes include a wide range of medical illnesses, with the highest number of excess deaths contributed by cardiovascular- and respiratory-related causes. This latter finding is consistent with previous research.[3,4]

Patients with schizophrenia show a similar increase in all-cause mortality, with the increased relative risk reported to be in the range of 1.5-fold to 3.3-fold higher than that of the general population.[4–6] As with affective illness, there is a significant increase in the mortality rate attributable to cardiovascular- and cerebrovascular-related causes.[5,6] Furthermore, there is evidence to suggest that the cardiovascular mortality rate may be increasing among people with schizophrenia.[7]

There is a wide array of variables that may potentially contribute to the increased mortality rates associated with major mental disorders such as schizophrenia and bipolar disorder. These variables can usefully be summarized in the following 4 categories: (1) shared diatheses/risk mechanisms, (2) suboptimal health behaviors secondary to the mental disorder, (3) poor health care access related to the mental disorder, and (4) treatment-related risks.

Shared Diatheses/Risk Mechanisms

Some of the increased mortality risk, especially risk of cardiovascular mortality, may be attributable to physiologic changes associated with unipolar or bipolar depression.[8] Depressive disorder has been associated with significant reduction in heart rate variability, which, in turn, has been identified as a significant risk factor for myocardial infarction.[9] Depression-related reduction in heart rate variability has been shown to be correlated with decreased vagal inputs in the heart.[10] Depression has also been associated with significant changes in platelet reactivity, which may increase the likelihood of clotting.[11]

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Finally, depression appears to be associated with altered immune activity[12] and hypothalamus-pituitary-adrenal (HPA) axis functioning,[13] both of which have been hypothesized to increase cardiovascular risk. Each of these physiologic mechanisms has varying degrees of scientific support, and their relative contribution to depression-related cardiovascular risk remains to be established.

Similarly, there is some evidence that patients with schizophrenia (compared to normal controls) may have impaired glucose metabolism that is present at the time of disease onset and prior to initiation of treatment.[14]

Suboptimal Health Behaviors

Major mental disorders are frequently associated with a wide range of behaviors that have a negative impact on health. For example, bipolar disorder and schizophrenia are associated with increased rates of human immunodeficiency virus and hepatitis C infection.[15] Bipolar disorder, unipolar depression, and schizophrenia are all associated with significantly increased risk of alcoholism and substance abuse, including smoking.[16] Schizophrenia is often associated with poor nutrition and reduced physical activity.[17]

Poor Health Care Access

Patients with major mental disorders frequently lack adequate insurance coverage and have poor access to high-quality health care.[18] Even when high-quality health care is available, access is fragmented, and the ability of the patient to follow through on treatment recommendations may be low.[19]

Treatment-Related Risks

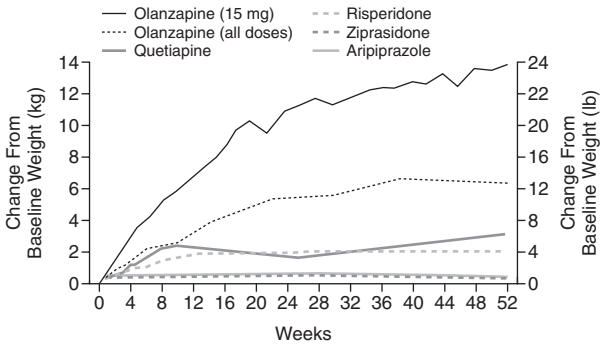
A final, important source of medical risk in major mental disorders is treatment itself. The subsequent sections of this article will briefly summarize the salient iatrogenic risks that influence treatment outcome.

TREATMENT AND WEIGHT GAIN

Obesity carries with it significant negative effects on health, especially cardiovascular health, though the cardiovascular risk associated with obesity appears to be largely due to correlated elevations in total cholesterol, low-density lipoprotein (LDL) cholesterol, and blood pressure and problems with glucose metabolism.[20]

Obesity has reached epidemic proportions in the Western world, with approximately 20% to 25% of adults meeting criteria for obesity (body mass index [BMI] ≥ 30 kg/m^2).[21] The age-adjusted incidence of obesity appears to be even higher in schizophrenia than in the general population, especially among women.[22] Similarly, there appears to be at least a 50% increase in the incidence of obesity among individuals with bipolar disorder, with more than one third of individuals meeting criteria for obesity.[23]

Figure 1. Mean Change in Weight During 52 Weeks of Treatment With Atypical Antipsychotics: Cross-Study Comparison[a]



[a]Data from Centers for Disease Control and Prevention,[24] Lebovitz,[25] and Newcomer.[14,26]

The precise extent and cause of the higher incidence of obesity in bipolar disorder and schizophrenia are uncertain. In part, this is due to the difficulty in disentangling the effect of treatment from underlying illness effects. Underlying illness effects may include lack of exercise and poor diet, as well as the possible (but unproven) presence of a genetic predisposition or physiologic factor that increases the risk for metabolic disturbance and obesity.[27]

It is now well established that many effective pharmacologic agents used to treat schizophrenia and bipolar disorder result in significant risk of weight gain.[28,29] Short-term treatment data (summarized in the package inserts)[30–32] indicate that the incidence of clinically significant weight gain ($\geq$ 7% gain) is higher (vs. placebo) for olanzapine (29% vs. 3%) compared to quetiapine (23% vs. 6%), risperidone (18% vs. 9%), ziprasidone (10% vs. 4%), or aripiprazole (8% vs. 3%). During long-term treatment, the mean change in weight is high for olanzapine, intermediate for quetiapine and risperidone, and minimal to none for ziprasidone and aripiprazole (Figure 1).[30–35]

The differential effect of treatment on weight is illustrated by head-to-head comparator trials[36] and by switch studies, which demonstrate the extent of weight loss when patients discontinue drugs that are associated with weight gain and start treatment with drugs less likely to result in weight gain.[37] The largest long-term trial (the 18-month Clinical Antipsychotic Trials of Intervention Effectiveness [CATIE][38]) found that clinically meaningful (> 7%) weight gain occurred in significantly more patients taking olanzapine (30%) versus quetiapine (16%), risperidone (14%), or perphenazine (12%) versus ziprasidone (7%) ($p < .001$ for the overall comparison).

Antipsychotic-associated weight gain appears to be highly correlated with affinity for the H_1 receptor, though activity at other receptors (e.g., α_1- and α_2-adrenergic

receptors, $5HT_{2c}$) has also been hypothesized to be involved.[28] The precise H_1 receptor mechanism that results in weight gain is unclear.

SCHIZOPHRENIA, GLUCOSE DYSREGULATION, AND DIABETES

The incidence of diabetes in the United States has been estimated to be approximately 3% to 5%, with higher rates observed in blacks and women.[24] Approximately 5% to 10% of individuals have type 1 diabetes (characterized by marked-to-total loss of insulin secretion by beta cells in the pancreas), while greater than 90% have type 2 diabetes, with progressively increased rates in older populations. Type 2 diabetes is the result of a combination of deficient insulin secretion coupled with insulin resistance at the insulin receptor.[25]

The incidence of diabetes appears to be at least 2-fold higher in both schizophrenia and bipolar disorder.[14,26] The etiology of glucose dysregulation in schizophrenia and bipolar disorder is likely to be multifactorial, but it is not simply secondary to obesity. This is illustrated by a careful study of drug-naive patients presenting with first-onset schizophrenia.[39] In this study,[39] there was no difference between patients with schizophrenia versus control subjects in BMI (24.5 kg/m^2 vs. 24.6 kg/m^2) or waist circumference (82.9 cm vs. 87.3 cm). However, among patients with schizophrenia, there was a significantly higher incidence of impaired fasting glucose tolerance (15.4% vs. 0%, $p < .02$), fasting insulin levels (9.8 vs. 7.7 μU/mL, $p < .05$), and fasting glucose levels (95.8 vs. 88.2 mg/dL, $p < .03$). Studies suggest that approximately one third of patients with schizophrenia and hyperglycemia go undiagnosed.[40]

The pathophysiologic mechanism underlying antipsychotic-associated glucose dysregulation is uncertain. Hypothesized mechanisms include interference with glucose transporter proteins, HPA axis overactivity, or indirect effects due to activity at presynaptic or postsynaptic monoaminergic receptors.[14]

Analyses of controlled clinical trials, supported by extensive data from pharmacovigilance studies, document a strong association between treatment with atypical antipsychotics and abnormalities in glucose metabolism.[14] There are significant differences in the risk of glucose dysregulation and iatrogenic diabetes among available antipsychotics. Treatment with clozapine and olanzapine is associated with higher levels of hyperglycemia (on glucose tolerance testing) and higher levels of insulin resistance on homeostasis model assessment compared to both conventional antipsychotics and to other atypicals (particularly aripiprazole and ziprasidone).[41,42] Treatment with risperidone and quetiapine is associated with a lower risk of hyperglycemia, while treatment with aripiprazole and ziprasidone is associated with the lowest risk of hyperglycemia, alterations in insulin sensitivity, or diabetes. Studies evaluating time to onset indicate that more than one third of treatment-emergent cases of hyperglycemia occur at 6 months or later.[14,43]

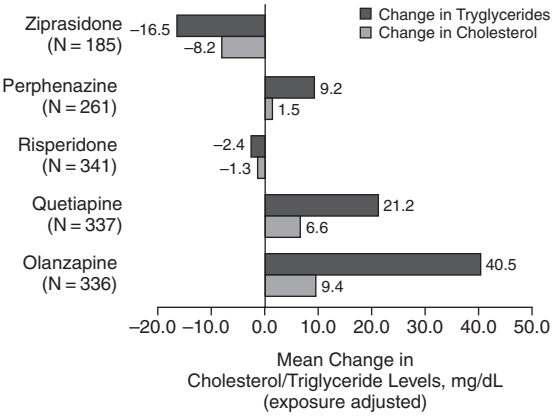
Experimental research on glucose regulation and insulin resistance suggests that the hyperglycemic effects of selected atypical antipsychotics may occur independently of weight gain.[44] This is confirmed by clinical reports of new-onset diabetes in patients who are not obese and/or who report no iatrogenic weight gain.[43,45]

EFFECT OF ATYPICAL ANTIPSYCHOTICS ON LIPIDS

Elevated LDL cholesterol (> 130 mg/dL) and triglyceride (≥ 200 mg/dL) and low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL) levels all represent independent cardiovascular risk factors.[46] A recent review[14] highlighted the absence of good data on how frequently dyslipidemia occurs in schizophrenia. Thus, it is not known whether patients with schizophrenia have a genetic diathesis that places them at risk when treated with atypical antipsychotics. Future research on this topic will need to control for the poor eating and exercise habits that have been reported to be more common in patients with schizophrenia and that may contribute indirectly to elevations in cholesterol and triglyceride levels.[27]

Data from case reports, pharmacovigilance studies, and controlled clinical trials document an association between treatment with selected atypical antipsychotics and changes in lipid levels.[14] As with the effects on weight and glucose metabolism, the risk of dyslipidemia is significantly higher in patients treated with olanzapine and clozapine. There is some evidence that treatment with risperidone and quetiapine may alter lipid levels, but results are conflicting, and the magnitude of the effect is smaller. In contrast, treatment with aripiprazole and ziprasidone has consistently shown minimal to no effect on lipids. This is illustrated by 2 double-blind, head-to-head comparator trials. In the first trial, 26 weeks of treatment resulted in significant elevations in total cholesterol and triglyceride levels with olanzapine but not aripiprazole, while HDL cholesterol levels significantly increased with aripiprazole but not olanzapine.[36] Similarly, 6 weeks of treatment also resulted in significant elevations in total cholesterol and LDL cholesterol levels with olanzapine but not ziprasidone; HDL cholesterol and lipoprotein levels were not significantly changed with either drug.[47] In three, 6-week, open-label studies,[48] switching from olanzapine or risperidone to ziprasidone resulted in significant reductions in plasma lipid levels, while switching from haloperidol had no significant effect. Finally, results from the CATIE trial (Figure 2)[38] provide comparator data on the effect of up to 18 months of treatment with 4 atypicals and 1 conventional antipsychotic. The results are consistent with previous studies and highlight the clinically significant effect on lipids of olanzapine and, to a lesser extent, quetiapine.[38]

Figure 2. Mean Change in Triglycerides and Total Cholesterol Levels: Results From Phase I of the CATIE Trial[a]



[a]Data from Lieberman et al.[38]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

SCHIZOPHRENIA, ATYPICAL ANTIPSYCHOTICS, AND THE METABOLIC SYNDROME

The metabolic syndrome is a constellation of clinical variables (abdominal obesity, dyslipidemia, hyperglycemia, hypertension) that significantly predict cardiovascular morbidity and mortality.[49] The increased cardiovascular mortality risk among individuals with metabolic syndrome has been estimated to range from 2.4-fold to 3.6-fold.[50,51]

The prevalence of metabolic syndrome in the United States has been estimated to be 24% in adults overall but shows a progressive increase with age, occurring in 5% of women and 7% of men 20 to 29 years of age, but in 44% of men aged 60 to 69 years.[52] The prevalence of metabolic syndrome in never-medicated patients with schizophrenia is unknown, but among naturalistic samples, the rate is significantly higher than in the general population, with estimates ranging from 41% to 63%.[53,54]

Pooled data from 2 double-blind, placebo-controlled trials[55] provide some of the first prospective data that have used metabolic syndrome as a (post hoc) safety outcome. The analysis found the cumulative incidence of treatment-emergent metabolic syndrome to be 19.2% with olanzapine, 12.8% with placebo, and 7.6% with aripiprazole (log rank p = .003).

The importance of metabolic effects secondary to treatment with atypical antipsychotics has led to monitoring recommendations cosponsored by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.[41] Current recommendations are as follows: BMI monthly for the first 3 months, then 4 times per year; waist circumference annually; and blood pressure, fasting glucose, and lipid profile at 3 months, then annually. More frequent monitoring may be appropriate in high-risk individuals (e.g., those with family history of diabetes or heart disease, already overweight, or hypertensive). A recent survey of 300 psychiatrists found much lower levels of monitoring practices, with 79% reporting that they rarely or never obtained waist circumference on their patients, while only 34% reported taking blood pressure readings on most or all of their patients.[56] Forty-three percent reported obtaining glucose levels, and 29% reported obtaining lipid levels for most or all of their patients.[56]

EFFECTS ON PROLACTIN

Hyperprolactinemia is estimated to occur in approximately 40% of men and 60% of women treated with conventional antipsychotics.[57,58] Estimates of prolactin-related side effects vary widely in the published literature, and while it is true that many cases of hyperprolactinemia are asymptomatic, menstrual irregularities (possibly iatrogenic) appear to occur in greater than 35% of women, and approximately 1 of 6 women reports galactorrhea.[59]

Other effects of hyperprolactinemia include reduction in sexual functioning (decreased libido, decreased arousal, anorgasmia—more common in males)[60] and possibly decreased bone density.[61] Amenorrhea and the possible effect on bone density are mediated by the indirect effect of elevated prolactin in reducing testosterone and estrogen levels that can occur in some patients.

The extent to which various antipsychotic agents influence prolactin levels varies greatly. As noted above, treatment with conventional antipsychotics is associated with dose-related increases in prolactin. Similar dose-related effects occur with risperidone. In contrast, olanzapine results in only transient elevations, while clozapine, quetiapine, ziprasidone, and aripiprazole have not been shown to increase prolactin.[59]

CENTRAL NERVOUS SYSTEM ADVERSE EVENTS: AKATHISIA AND SOMNOLENCE

Akathisia

Prior to the advent of atypical antipsychotics, akathisia was perhaps the most frequent and distressing of the acute drug-induced movement disorders, occurring in approximately 1 of 4 patients. Akathisia is associated with treatment nonadherence. The CATIE trial[38] provides a useful head-to-head comparison of the incidence of clinically significant akathisia (Barnes Akathisia Rating Scale global score ≥ 3): ziprasidone, 9%; risperidone, 7%; perphenazine, 7%; olanzapine, 5%; and quetiapine, 5%. Discontinuations due to any extrapyramidal side effect in CATIE were significantly higher with perphenazine (8%)

compared to all atypicals (2%–4%). Aripiprazole was not included in the CATIE study, but it is associated with a 10% rate of akathisia (compared to 4% of placebo-treated patients) in short-term trials.[32]

Somnolence

Sedation is an important adverse drug effect, but one that may have therapeutic benefit if insomnia is an element of the clinical presentation. Sedation, however, may have other negative consequences, including increased risk of falls or injuries, impairment in cognitive and psychomotor functioning, and an overall reduction in ability to function.[62] Sedation may limit the ability to achieve therapeutic dosages and increases the risk of nonadherence.

Sedation due to antipsychotic therapy is thought to be largely due to antagonist activity at the histamine (H_1) receptor. The risk of sedation correlates fairly well with the affinity (Ki) for the H_1 receptor. Among atypical antipsychotics,[63,64] clozapine (Ki, 1.8), olanzapine (Ki, 2.8), and quetiapine (Ki, 8.7) have the highest incidence of sedation (48%, 29%, and 18%, respectively, based on data reported in the package inserts[65–67]); aripiprazole (Ki, 61) and ziprasidone (Ki, 47) have the lowest incidence (12% and 14%). For conventional antipsychotics, sedation ranges from mild to severe.[68]

SUMMARY

Atypical antipsychotics may have some efficacy advantages over conventional antipsychotics, but any differences in efficacy are modest, both between class and within class. In contrast, the magnitude of the differences in safety and tolerability is larger and may have a greater influence on clinical outcome. As such, choice of which antipsychotic to prescribe should always take into consideration each drug's safety and tolerability profile.

The safety and tolerability of antipsychotics are especially important because of the chronicity of the illnesses being treated, the need for long-term therapy, and the poor insight and motivation of many of the patients. Cardiovascular safety is of paramount importance because patients diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder are at high risk to begin with.

In conclusion, an evidence-based conceptual framework for decision making is required that takes into account the likelihood of a safety issue (e.g., metabolic syndrome) occurring, the patient's unique vulnerability to developing specific adverse events, the reversibility and manageability of these safety events, and the long-term health consequences of persistence of a side effect with safety-related concerns. Future prospective research needs to include patient-centered measures that evaluate the impact of safety events on adherence, quality of life, functioning, and global health.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, 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 that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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