ABSTRACT

Second-generation, or atypical, antipsychotic drugs, have fewer central nervous system side effects, such as extrapyramidal symptoms and tardive dyskinesia, compared with conventional antipsychotic drugs. However, these newer agents are often associated with drug-specific metabolic side effects, such as weight gain, dyslipidemia, and glucose abnormalities that carry an increased risk of diabetes, and hyperprolactinemia. Each atypical antipsychotic agent has a different adverse-effect profile. Prescribing choices should be based on the medication that causes the least number of adverse effects for a patient while maintaining efficacy. (Adv Stud Nurs. 2004;2(1):16-23)

SIDE EFFECTS OF ATYPICAL ANTIPSYCHOTIC AGENTS

EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal symptoms are thought to be the result of dopamine blockade in the nigrostriatal pathway, an area of the brain associated with the regulation of movement and coordination of reflexes. Extrapyramidal symptoms comprise 4 main areas of motor dysfunction: tardive dyskinesia, Parkinsonism, akathisia, and dystonia.

Patients may also develop neuroleptic malignant syndrome (NMS), a rare but serious condition typified by hyperthermia; muscle rigidity; tachycardia; hypoxia; altered mental status, confusion, or coma; and serious metabolic changes. NMS is potentially fatal and requires intensive emergency care.
Extrapyramidal symptoms are often distressing to patients. In a survey of 99 patients taking antipsychotic medication, more patients considered akinesia as being moderately-to-severely distressing compared with other side effects (40%); however, concern with akinesia was closely followed by moderate-to-severe distress associated with weight gain (37.3%), anticholinergic effects (33.2%), and sexual dysfunction (30.8%). Although extrapyramidal symptoms are more commonly affiliated with the older typical neuroleptic agents, they are also observed in patients taking atypical medications, especially at higher doses (Figure 1).

Anecdotal reports and small trials comparing drugs suggest that the incidence of extrapyramidal symptoms varies among the atypical antipsychotic agents; conclusions cannot be made, however, without well-designed head-to-head studies comparing all of the agents. A Cochrane Collaboration review of new atypical antipsychotic drugs versus clozapine reported that although clozapine produced more fatigue, hypersalivation, nausea, and orthostatic dizziness, the new atypical drugs, with the exception of olanzapine, produced more extrapyramidal symptoms.8

Aripiprazole, which was not included in the aforementioned review, is a new atypical antipsychotic agent that combines partial agonist activity at dopamine D2 receptors and serotonin 5-HT1A receptors with antagonist activity at serotonin 5-HT2A receptors.10 This mechanism is unique from other atypical antipsychotic drugs, and studies suggest that aripiprazole may have a different adverse-event profile compared with these other agents.

Supporting this notion is a study by Marder and colleagues, which analyzed safety and tolerability data from 5 short-term placebo-controlled clinical trials of aripiprazole.10 Aripiprazole (from 2 mg to 30 mg daily) was found to be no different from placebo on the Simpson-Angus Scale (SAS), a commonly used measure of extrapyramidal symptoms. There was no dose-dependent effect on akathisia as measured by the Barnes Akathisia Rating Scale (BARS). Findings did show a significant reduction in Abnormal Involuntary Movement Scale (AIMS) scores from baseline compared with placebo (P < .001). In contrast, haloperidol showed significantly increased SAS and BARS scores compared with placebo (P ≤ .01). A long-term study (52 weeks) by Kasper and colleagues showed that aripiprazole was associated with significantly less extrapyramidal symptoms as shown by measures of Parkinsonism (SAS; P < .0001), akathisia (BARS; P < .001), and tardive dyskinesia (AIMS; P < .001). The investigators used a last observation carried forward analysis—the last score of a patient who drops out of the study is recorded as the score for the remaining time points, as if the patient had completed the trial.

**Weight Gain**

Some antipsychotic agents have a tendency to induce weight gain, which raises clinical concern for 2 primary reasons: increased body weight is a significant risk factor for comorbid conditions, such as type 2 diabetes, dyslipidemia, hypertension, and coronary heart disease; and the stigma associated with obesity is a significant factor in causing nonadherence to therapy. The stigma associated with weight gain should not be underestimated. Patients will sometimes choose to tolerate psychotic symptoms rather than gain weight by taking antipsychotic medication.12

Weight gain was first observed with the neuroleptics in the late 1950s but was considered unimportant compared with the severe extrapyramidal symptoms and tardive dyskinesia these agents caused.13 Second-generation antipsychotic medications are also associated with weight gain, but the magnitude varies from agent to agent.
Mclntyre and colleagues propose several mechanisms of antipsychotic-induced weight gain, all of which are under active study. Antipsychotic drugs are antagonists of monoamine receptors, many of which mediate appetite. They also act against histamine, which is thought to stimulate appetite and increase eating. Conventional antipsychotic agents elevate prolactin levels and may promote weight gain by disrupting androgen and estrogen balance. Atypical agents may also interact with other neurotransmitter systems instrumental in regulating appetite and metabolism, such as gamma-aminobutyric acid, glutamate, neuropeptides (eg, insulin, neuropeptide Y), and cytokines (eg, tumor necrosis factor-alpha, interleukin-2, leptin). Further research is needed to clarify the mechanisms of atypical antipsychotic drug-induced weight gain.

Allison and colleagues conducted a comprehensive review of the literature to determine the differences between novel antipsychotic agents in their propensity to induce weight gain and found a wide range of variability. Among conventional agents, the mean weight change ranged from a reduction of 0.39 kg with molindone to an increase of 3.19 kg with thioridazine. Differences also occurred in weight gain among the newer antipsychotic agents (clozapine, 4.45 kg; olanzapine, 4.15 kg; sertindole, 2.92 kg; risperidone, 2.10 kg; ziprasidone, 0.04 kg). Placebo was associated with a mean weight reduction of 0.74 kg. In a pooled analysis of safety and tolerability data from all 5 short-term (4 to 6 weeks) placebo-controlled trials in patients hospitalized with acute relapse of schizophrenia or schizoaffective disorder, aripiprazole was found to induce minimal weight gain, similar to placebo (0.71 kg).

Using data from the product labels to compare clinically significant weight gain (≥7% of body weight) associated with these newer agents, the difference between agents is again evident, with aripiprazole having the least effect on weight gain and olanzapine the greatest (Figure 2).

### DIABETES

Weight gain is a major risk factor for type 2 diabetes. Results from a prospective cohort study involving more than 114,000 middle-aged women between 1976 and 1990 showed that body mass index (BMI) was the predominant predictor of risk for diabetes mellitus. Risk increased with increase in BMI, even in women with average weight (BMI = 24.0 kg/m²). However, risk of diabetes increased exponentially for obese women (BMI ≥30 kg/m²). In contrast, women who lost more than 5.0 kg reduced their risk of diabetes by 50% or more. These results were independent of family history of diabetes.

A consensus statement was recently released 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. According to the statement, overall, the limited amount of epidemiologic data suggest an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes in people with psychiatric illness. Whether this is a function of the illness itself or the treatment is unknown. Studies using the proper diagnoses of glucose intolerance and more complete risk-factor characterization are needed.

A study conducted in 1956 reported a 4.2% prevalence rate of type 2 diabetes in the schizophrenia population not taking antipsychotic treatment. In 1968, 3 years after the introduction of phenothiazine, the prevalence increased to 17.2%. In most studies during that time, prevalence rates ranged from 11% to 18%. By comparison, the prevalence of type 2 diabetes in the general population of individuals between 18 and 44 years of age is 1.2%.

Lindenmayer and colleagues reported that case reports, chart reviews, and results from clinical drug trials implicate a relationship between glucose levels and treatment with clozapine or olanzapine in patients with schizophrenia. The report also indicated that a few cases...
of hyperglycemia have been reported in patients taking risperidone and quetiapine. According to the results of these studies, antipsychotic drug–associated hyperglycemia is not dose dependent and is reversible with cessation of treatment. Possible mechanisms include a combination of decreased sensitivity to insulin independent of atypical medication, increased insulin resistance related to atypical medication, effects of atypical medications on serotonin receptors, and weight gain. Data are limited, however, and Lindenmayer notes that it is difficult to statistically assess the true incidence of diabetes within each type of antipsychotic medication group by depending exclusively on available case studies and without performing proper epidemiologic research.

Koro and colleagues conducted a large, population-based, nested, case-control study to quantify the risk of diabetes associated with conventional and newer-generation antipsychotic medications, specifically olanzapine and risperidone. Patients taking olanzapine had a significantly increased risk of developing diabetes compared with patients not taking antipsychotic drugs (odds ratio [OR], 5.8; 95% confidence interval [CI], 2.0-16.7) or patients taking conventional antipsychotic drugs (OR, 4.2; 95% CI, 1.5-12.2). Risk was lower with risperidone; patients taking risperidone had a nonsignificant increased risk of diabetes compared with patients not taking antipsychotic drugs (OR, 2.2; 95% CI, 0.9-5.2) or those taking conventional antipsychotic drugs (OR, 1.6; 95% CI, 0.7-3.8).

Wirshing and colleagues measured the blood glucose levels of patients before and after therapy with various antipsychotics and found a statistically significant increase in blood glucose levels in patients before and after therapy with antipsychotic drugs (OR, 1.6; 95% CI, 0.7-3.8). A recent 26-week placebo-controlled study of aripiprazole showed no clinically significant changes in blood glucose in patients taking aripiprazole. Glucose levels were comparable to placebo throughout the trial.

**Dyslipidemia**

Several reports indicate that dibenzodiazepine-derived antipsychotic medications (eg, olanzapine, quetiapine, clozapine) may significantly elevate fasting lipid levels. Dyslipidemia is a concern due to the long-term implications regarding increased cardiovascular risk. Meyer conducted a retrospective study of patients taking risperidone (n = 47) or olanzapine (n = 47) for 1 year and found that both drugs were associated with increased triglyceride levels compared with baseline levels. However, patients younger than 60 years of age who were taking olanzapine experienced significantly greater increases in triglycerides, total cholesterol levels, and glucose levels compared with patients in the same age group who were taking risperidone. These effects were independent of changes in weight.

Clozapine, in particular, is known to cause elevated triglyceride levels. Gaulin and colleagues examined the medical records of 222 inpatients treated with clozapine or haloperidol and found that men taking clozapine had significantly higher follow-up serum triglyceride concentrations over baseline compared with those taking haloperidol. Women experienced serum triglyceride elevations regardless of treatment with clozapine or haloperidol. Spivak and colleagues examined 70 patients with schizophrenia who were resistant to neuroleptics and were treated with clozapine for at least 6 months and 30 patients with chronic schizophrenia taking conventional antipsychotic agents for the same length of time. Clozapine was associated with an elevation in serum triglyceride levels, whereas conventional antipsychotic agents were associated with an elevation in serum total cholesterol levels. Ghaedi and Dufresne reported that psychotic patients who were switched from clozapine to risperidone then back to clozapine experienced elevated triglycerides with clozapine therapy both times.

In a study by Koro and colleagues, which included more than 13 000 patients with schizophrenia in a large UK healthcare database, olanzapine was associated with nearly a 5-fold increase in the risk of developing hyperlipidemia compared with no antipsychotic drug exposure (OR, 4.65; 95% CI, 2.44-8.85; P < .001) and more than a 3-fold increase compared with use of conventional agents (OR, 3.36; 95% CI, 1.77-6.39; P < .001). Risperidone was not associated with increased hyperlipidemia compared with patients taking no treatment or those taking conventional antipsychotic medications. In a study by Pigott and colleagues, aripiprazole was not associated with changes in total cholesterol, low-density lipoprotein, high-density lipoprotein, or triglycerides compared with placebo. At the 2003 American Psychiatric Association annual meeting, McCue reported that aripiprazole was consistently and significantly better than olanzapine at maintaining levels of serum lipids comparable to levels in patients taking placebo.
HYPERPROLACTINEMIA

Prolactin secretion is regulated by dopamine secretion in the tuberoinfundibular tract and the hypothalamo-hypophyseal vessels. Hyperprolactinemia is a common side effect of antipsychotic therapy—especially with conventional agents—and can lead to adverse effects on menstruation (eg, anovulation, shortened luteal phase, oligomenorrhea, amenorrhea), breast health (eg, engorgement, galactorrhea, cancer), bone density (leading to osteoporosis), sexual function (eg, decreased libido, orgasmic dysfunction), and venous thromboembolism.31 One possible explanation for this phenomenon is that antipsychotic agents inhibit dopamine action at D2 receptors, thereby disrupting the regulation of prolactin production.32 Most atypical agents introduced over the past decade do not elevate prolactin levels; however, some do. In a 28-week study of risperidone and olanzapine, Tran and colleagues reported that 51% of patients had elevated prolactin during the study, but the incidence declined to 36% by the end of the study.33 In a study comparing the effects of clozapine, olanzapine, risperidone, and haloperidol, Volavka and colleagues found that risperidone caused significant elevation of prolactin levels (P < .05) that appeared to be dose dependent.34 Kleinberg and colleagues compiled data from all randomized double-blind studies of risperidone in patients with chronic schizophrenia to characterize the relationship between risperidone, serum prolactin levels, and possible clinical sequelae.35 Both risperidone and haloperidol produced dose-related increases in plasma prolactin levels in men and women. In women, risperidone dose was not correlated with adverse events, and adverse events were not correlated with endpoint prolactin levels. Among men, the incidence of adverse events was positively correlated with risperidone dose; however, at doses of 4 mg to 10 mg daily, the incidence of adverse events was not significantly higher compared with patients taking placebo. The authors reported that adverse events in men were unrelated to plasma prolactin levels and concluded that a risperidone-associated increase in serum prolactin was not significantly correlated with the emergence of possible prolactin-related side effects. Data compiled from short- and long-term studies of aripiprazole show that the agent has no effect on prolactin levels.10

CLINICAL IMPLICATIONS

Most psychiatric nurses are familiar with the sedation, cognitive dysfunction, fatigue, extrapyramidal symptoms, tardive dyskinesia, and other CNS side effects induced by conventional antipsychotic medications, such as chlorpromazine and haloperidol. Despite these drawbacks, these agents remain useful for specific patients and situations, such as for rapid symptom control in the acute-care setting or when a depot medication is required because oral medication is not the best choice. Intramuscular preparations of ziprasidone and olanzapine have recently become available and are indicated for the treatment of acute agitation associated with schizophrenia (ziprasidone and olanzapine) and bipolar mania (olanzapine). These newer agents rapidly reduce agitation with fewer extrapyramidal side effects.

The new-generation antipsychotic agents require that nurses better understand and use them appropriately for long-term disease management based on their side-effect profiles, patient risk for metabolic effects, and patient treatment goals. The first step in long-term management is to establish a trusting nurse/patient relationship. It is also essential for nurses to recognize and treat potential metabolic side effects, which are sometimes subtle. Suggested methods for managing these side effects are as follows:

EXTRAPYRAMIDAL SYMPTOMS

• Although extrapyramidal symptoms are less of a problem with atypical antipsychotic agents, they can occur at higher doses. If these symptoms occur, consider lowering the dose or switching medications.
• Assess and document baseline movement status.
• If the drug is desired, interventions should be implemented to reduce the impact of these side effects: reassure the patient that symptoms are not a worsening of the psychiatric condition but a treatable side effect of medication; assure the patient you will be responsive to changes in symptoms; decrease stressful situations, which can increase symptoms; ensure the patient receives adequate rest; assist the patient in maintaining nutrition and hydration if necessary.

WEIGHT GAIN

• Establish a baseline weight and BMI.
• Discuss the patient’s satisfaction with or concerns about present weight and potential for weight gain.
• Advise the patient of the likelihood for weight gain and immediately begin a program of weight monitoring and counseling. Educating the patient on weight monitoring (times, amounts, activities, and feelings) is essential.
• If a patient refuses to take a medication because it causes weight gain, counsel him or her about the importance of having psychosis under control (eg, adequate symptom control, increased functioning, self-sufficiency, stability in relationships, financial stability). Reassure the patient that other steps can be taken to prevent weight gain. Work with the patient to analyze weight data, look for patterns of eating and activities, develop realistic strategies for changing behavior, and set goals. Refer the patient to a specialist if necessary.
• If weight gain becomes an intractable problem and will not resolve through counseling or other methods, consider switching medications to one that has a lesser probability of inducing weight gain, keeping in mind the importance of balancing the antipsychotic efficacy with the discomfort and seriousness of the side effect. Drug-drug interactions also need to be considered.

**DIABETES**
• Assess the patient for diabetes risk before treatment (eg, family history, BMI, sedentary lifestyle).
• Based on family history and risk factors, consider regular monitoring for hyperglycemia before and throughout treatment (include fasting glucose in baseline laboratory tests).
• Educate the patient and family about the signs and symptoms of diabetes, particularly polydipsia, polyphagia, and polyuria.
• If diabetes develops, consider switching medications to one with a lesser probability of inducing hyperglycemia.

**DYSLIPIDEMIA**
• Assess the patient for risk of dyslipidemia before treatment (eg, family history of dyslipidemia or heart disease, overweight, diabetes).
• Obtain fasting lipid levels, including triglycerides, before treatment.
• Monitor lipid levels regularly throughout treatment.
• Advise the patient of the risk for developing dyslipidemia and suggest dietary counseling with a dietitian or nutritionist.
• If necessary, treat the patient with medications that treat hyperlipidemia.

**HYPERPROLACTINEMIA AND SEQUELAE**
• Obtain baseline prolactin levels.
• Monitor the patient closely for hyperprolactinemia during treatment.
• Watch patients carefully for signs of hyperprolactinemia, such as gynecomastia.
• Assess for gynecomastia; encourage patients to discuss sensitive issues, such as gynecomastia and sexual dysfunction. This especially refers to men.
• Pay attention to your female patients if they tell you that they feel they are pregnant. This may be amenorrhea and/or galactorrhea due to hyperprolactinemia and not a psychotic delusion.
• Consider switching medications if symptoms of hyperprolactinemia are affecting the patient’s quality of life.

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**Reference Values for Monitoring Side Effects of Antipsychotic Therapy**

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<thead>
<tr>
<th><strong>SIDE EFFECT</strong></th>
<th><strong>REFERENCE VALUE</strong></th>
</tr>
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<tbody>
<tr>
<td><strong>BMI</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Normal, 18.5–24.9 kg/m²; overweight, 25–29.9 kg/m²; obese, ≥30 kg/m²</td>
</tr>
<tr>
<td>Fasting blood glucose&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Normal, &lt;100 mg/dL; impaired fasting glucose, 100–125.9 mg/dL; diabetes, ≥126 mg/dL</td>
</tr>
<tr>
<td>Fasting lipids&lt;sup&gt;18&lt;/sup&gt; LDL</td>
<td>Optimal, &lt;100 mg/dL; near/above optimal, 100–129 mg/dL; borderline high, 130–159 mg/dL; high, 160–189 mg/dL; very high, ≥190 mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Desirable, &lt;200 mg/dL; borderline high, 200–239 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>Low, desirable, &lt;40 mg/dL; high, ≥60 mg/dL</td>
</tr>
<tr>
<td>Prolactin&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Women: 3.4–24.1 µg/mL; Men: 4.1–18.4 µg/mL</td>
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</table>

<sup>*</sup> Ranges vary according to laboratory and assay.
**CONCLUSION**

The atypical antipsychotic drugs have brought us beyond the era in which patients had to endure severe extrapyramidal symptoms and tardive dyskinesia. In this sense, they are "cleaner" drugs. However, these agents do have other associated adverse metabolic and endocrine adverse effects that must be recognized and managed.

The continuing development of new antipsychotic drugs is providing new options for patients who may be unable to maintain their regimen because of side effects but present new challenges in terms of metabolic and other side effects that may affect adherence.

**REFERENCES**


11. Kasper S, Lerman M N, M cQ uade RD et al. Efficacy and safety of aripiprazole vs haloperidol for long-term mainte-


