Primary Care Issues in Patients with Mental Illness

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Family physicians commonly care for patients with serious mental illness. Patients with psychotic and bipolar disorders have more comorbid medical conditions and higher mortality rates than patients without serious mental illness. Many medications prescribed for serious mental illness have significant metabolic and cardiovascular adverse effects. Patients treated with second-generation antipsychotics should receive preventive counseling and treatment for obesity, hyperglycemia, diabetes, and hyperlipidemia. First- and second-generation antipsychotics have been associated with QT prolongation. Many common medications can interact with antipsychotics, increasing the risk of cardiac arrhythmias and sudden death. Drug interactions can also lead to increased adverse effects, increased or decreased drug levels, toxicity, or treatment failure. Physicians should carefully consider the risks and benefits of second-generation antipsychotic medications, and patient care should be coordinated between primary care physicians and mental health professionals to prevent serious adverse effects. ***(Am Fam Physician.*** **2008;78(3):355-362, 363-364. Copyright © 2008 American Academy of Family Physicians.)**

▶ **See related editorial on page 314.**

▶ **Patient information:** A handout on mental illness, written by the authors of this article, is provided on page 363.

Serious mental illness (i.e., schizophrenia, nonaffective psychotic disorders, bipolar spectrum disorders, substance dependence, and suicidality) affects 6 percent of adults in the United States.[1] Patients with these disorders have a higher risk of mortality associated with clinical disease and unnatural causes (e.g., suicide, homicide, accidents).[2,3] Common medical conditions in patients with serious mental illness include metabolic disorders, cardiovascular disease, chronic pulmonary disease, gastrointestinal disorders, and obesity.[4,5]

Historically, efforts to improve the health of patients with mental illness focused solely on pharmacologic treatment. However, recent efforts have also included medical comorbidities and quality of medical care.[6,7]

Causes of Poor Health

Several factors contribute to poor health and increased mortality in patients with serious mental illness. These patients may have decreased access to health insurance and medical care and may delay seeking care because of cost.[8] One study showed that persons with mental illness were less likely to receive preventive care, including cancer screening, tobacco-use counseling, and immunizations.[6] Patients with mental illness are also less likely to receive appropriate treatment for acute problems, such as coronary revascularization procedures following an acute myocardial infarction.[9]

A study that surveyed family physicians about patients with common complaints (severe headache or abdominal pain) and comorbid mental illness showed that physicians underestimate the pretest probability of disease and, consequently, obtain fewer appropriate tests.[10] Patients with mental illness who have been diagnosed with diabetes and hyperlipidemia are only 29 percent as likely to be prescribed a statin medication as patients without mental health problems.[11] Patients with mental illness report poor coordination of care between primary care physicians and mental health professionals.[12] Lifestyle and behavioral factors also contribute to increased comorbidities in these patients. Patients with schizophrenia in particular have poorer dietary habits, smoke more, and exercise less than the general population.[13,14]

Medication adverse effects and interactions contribute to medical comorbidities.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Patients using second-generation antipsychotics should receive counseling to prevent obesity, hyperlipidemia, and diabetes.*	C	24
When possible, primary care physicians should avoid prescribing drugs that interact with psychiatric medications in patients with serious mental illness.	C	19, 33-35
To avoid medication-related adverse outcomes, primary care physicians and mental health professionals should coordinate the care of patients with serious mental illness.	C	47

**—Recommendation from consensus guidelines of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity.*

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see http://www.aafp.org/afpsort.xml.

Primary care physicians and mental health professionals may not be aware of each medication these patients have been prescribed, increasing the risk of interactions. Many common psychiatric medications *(Table 1)* cause serious adverse effects. First-generation antipsychotics cause extrapyramidal adverse effects, including tardive dyskinesia, whereas second-generation antipsychotics may cause metabolic adverse effects, including weight gain, obesity, glucose intolerance, diabetes, and hyperlipidemia. Both antipsychotic classes are associated with cardiovascular adverse effects, particularly QT prolongation.

Table 1. Common Antipsychotic Medications

First-generation antipsychotics*
Chlorpromazine (Thorazine†)
Fluphenazine (Prolixin†)
Haloperidol (Haldol)
Loxapine (Loxitane)
Mesoridazine (Serentil); this medication has been discontinued in the United States
Molindone (Moban)
Perphenazine (Trilafon†)
Pimozide (Orap)
Prochlorperazine (Compro)
Thioridazine (Mellaril†)
Thiothixene (Navane)
Trifluoperazine (Stelazine†)

Second-generation antipsychotics‡
Aripiprazole (Abilify)
Clozapine (Clozaril)
Olanzapine (Zyprexa)
Paliperidone (Invega)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Ziprasidone (Geodon)

**—Also called typical antipsychotics; associated with an increased incidence of extrapyramidal symptoms and increased cognitive impairment.*
†—Brand no longer available in the United States.
‡—Also called atypical antipsychotics; associated with a decreased incidence of extrapyramidal symptoms.

OBESITY AND WEIGHT GAIN

Obesity associated with serious mental illness is multifactorial.[5] Medication effects, poor nutrition, difficulty with meal planning, poor impulse control, and lack of exercise contribute to weight gain.[15] Second-generation antipsychotics can cause rapid weight gain in the first few months of therapy *(Table 2*[16-19]*)*, and it can take up to one year for body weight to stabilize. Average weight gain varies from 1 lb, 2 oz (0.5 kg) to 11 lb (5.0 kg) within the first 10 weeks of therapy. The mechanism of antipsychotic-induced weight gain is unknown.

DIABETES

Before the availability of antipsychotic medications, the prevalence of diabetes in patients with schizophrenia was estimated at 2.5 to 4.2 percent.[20] A recent cross-sectional study of patients in Holland with schizophrenia and schizoaffective disorder, showed that the prevalence of hyperglycemia and diabetes are 7.0 and 14.5 percent, respectively.[21]

The increased risk of type 2 diabetes in patients with schizophrenia or bipolar disorder is associated with the increased use of second-generation antipsychotics.[22,23]

Although the exact mechanism for hyperglycemia is unknown, it may be caused by drug-induced insulin resistance from associated weight gain, changes in body fat distribution, or direct effects on insulin-sensitive target tissues.[24]

New-onset diabetes, worsening of known diabetes, and hyperglycemic crises have been reported after the initiation of second-generation antipsychotics. The U.S. Food and Drug Administration requires that labels for all second-generation antipsychotics include warnings about the risk of hyperglycemia and diabetes. Clozapine (Clozaril) and olanzapine (Zyprexa) are associated with the greatest risk. Clinical trials of ziprasidone (Geodon) and aripiprazole (Abilify) lasting up to one year demonstrated rates of weight gain and metabolic changes similar to that of placebo.[25]

HYPERLIPIDEMIA

Second-generation antipsychotics are associated with increased serum triglyceride and total cholesterol levels. Clozapine appears to have the strongest effect, increasing triglyceride levels by up to 42 percent. Olanzapine has been associated with a 38 percent increase in triglyceride levels and a 10 percent decrease in high-density lipoprotein (HDL) cholesterol levels, with the maximal effect occurring within 10 months of initiating therapy. Quetiapine (Seroquel) increases triglyceride levels by 17 percent and may decrease HDL cholesterol levels. Risperidone's (Risperdal) effect on lipid levels is unclear.[26] Aripiprazole and ziprasidone have not been shown to have significant effects on lipid levels.[26] There is no conclusive evidence that these changes in lipid profiles lead to increased cardiovascular events.[27]

Table 2. Selected Antipsychotics Associated with Weight Gain

Medication	*Effect on weight gain*
First-generation antipsychotics	Weight gain is generally less than with second-generation antipsychotics, but the effects are widely variable
Second-generation antipsychotics*	
Aripiprazole (Abilify)	Similar to placebo[16]
Clozapine (Clozaril)	Average weight gain at 10 weeks: 9 lb, 13 oz (4.45 kg)[17,18]
Olanzapine (Zyprexa)	Average weight gain at 10 weeks: 9 lb, 2 oz (4.15 kg)[17,18]
Quetiapine (Seroquel)	Weight gain ranges from minimal to a mean gain of 5 lb, 8 oz (2.49 kg) at six weeks[17]
Risperidone (Risperdal)	Average weight gain at 10 weeks: 4 lb, 10 oz (2.10 kg)[17,18]
Ziprasidone (Geodon)	Average weight gain at 10 weeks: 1 oz (0.04 kg)[18]

**—Combining second-generation antipsychotics with mood stabilizers, particularly lithium and valproate (Depacon), leads to additional weight gain.[19]*

Information from references 16 through 19.

Guidelines for the Prevention and Treatment of Metabolic Changes

The American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity convened a consensus panel in November 2003 to develop guidelines for the prevention and treatment of metabolic changes induced by antipsychotic therapy.[24] The following section summarizes the panel's recommendations on lifestyle counseling, obesity management, patient education, and treatment goals. The recommended monitoring protocol for patients receiving second-generation antipsychotics is summarized in *Table 3*.[24]

EXERCISE AND WEIGHT MANAGEMENT

Patients with serious mental illness are more likely to be physically inactive than the general population. Factors associated with physical inactivity include female sex and limited social contacts.[13] All patients with mental illness treated with second-generation antipsychotics should receive physical activity counseling, and those who are overweight or obese should also receive nutrition counseling.

If a patient's weight increases by more than 5 percent, physicians should consider changing, using slow cross-titration, to another second-generation antipsychotic that is not associated with weight gain.[24] If possible, patients should be referred to a weight management program specifically tailored to patients with serious mental illness.

Table 3. Monitoring Recommendations for Patients Receiving Second-Generation Antipsychotics

	Frequency of assessment						
Assessment	*Baseline*	*Four weeks*	*Eight weeks*	*12 weeks*	*Quarterly*	*Annually*	*Every five years*
Review personal and family history	X					X	
Weight (body mass index)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose level	X			X		X	
Fasting lipid profile	X			X			X

NOTE: *Table reflects the minimum frequency of assessments; more frequent monitoring may be appropriate in select patients based on underlying conditions and family history.*

Adapted with permission from American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. *2004;27(2):599.*

DRUG SELECTION

When prescribing a second-generation antipsychotic, physicians should inform patients and their caregivers about the risk of adverse metabolic effects and educate them about the signs and symptoms of diabetes. Patients with risk factors for diabetes, who have a diagnosis of diabetes, or who are taking other medications associated with weight gain may benefit from aripiprazole or ziprasidone therapy, which cause less weight gain than other medications. The panel recommends that patients who develop worsening hyperglycemia or dyslipidemia during therapy be switched to a second-generation antipsychotic that has not been associated with significant weight gain or diabetes. The benefits of continuing effective psychiatric medications should be balanced with the patient's cardiovascular risk and the ability to achieve diabetes treatment goals.

The ADA's therapeutic goals for blood pressure, lipid levels, glycemic control, and monitoring in the general population also apply to patients with serious mental illness. However, patients with mental illness are less likely to receive recommended interventions.[28,29] Although physicians should not alter therapeutic goals based only on the presence of a serious mental illness, they should prioritize therapy based on the patient's psychiatric status.

Cardiovascular Disease and QT Prolongation

Rates of cardiovascular and cerebrovascular diseases are higher in patients with schizophrenia compared with the general population.[2] The calculated 10-year risk of coronary heart disease in patients with schizophrenia is 50 percent higher in women and 34 percent higher in men, compared with the general population. This increased risk may be partially caused by lifestyle factors; however, the metabolic effects of antipsychotic medications also may contribute.[30] Physicians tend to treat risk factors for cardiovascular disease less aggressively in patients with diabetes who have serious mental illness compared with those who do not have mental illness.[11]

The use of antipsychotics, even at low doses, is associated with a threefold increase in the risk of cardiac sudden death in outpatients.[31] QT prolongation is associated with ventricular arrhythmias, which can cause syncope, ventricular fibrillation, and sudden death.[32] First- and second-generation antipsychotics have been associated with QT prolongation to varying degrees. The antipsychotic thioridazine (Mellaril; brand no longer available in the United States) has the greatest effect on the QT interval, followed by ziprasidone, haloperidol (Haldol), quetiapine, risperidone, and olanzapine.[19] Aripiprazole has not been shown to cause QT prolongation.[33]

Medications known to cause QT prolongation *(Table 4[34])* should be avoided in patients with heart disease, history of syncope, family history of sudden death at any age, drug or alcohol abuse, personal or family history of congenital long QT syndrome, or electrolyte imbalances as well as in older women. For more information about medications associated with QT prolongation, go to http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.cfm.

Medications that can cause QT prolongation should not be prescribed concurrently. Medications that inhibit the metabolism of antipsychotic agents should be avoided, if possible. However, if these medications are prescribed, physicians should use caution because the effects on the QT interval appear to be related to increased serum drug concentrations.[35]

Performing baseline electrocardiography (ECG) before initiating antipsychotic therapy is controversial. However, ECG can identify patients with preexisting QT prolongation. Monitoring electrolyte and magnesium levels is suggested in patients receiving thioridazine or ziprasidone who are at risk of electrolyte deficiencies.[36]

Table 4. Selected Medications Associated with QT Prolongation

Amiodarone (Cordarone)
Clarithromycin (Biaxin)
Digoxin
Disopyramide (Norpace)
Droperidol (Inapsine)
Erythromycin
Flecainide (Tambocor)
Fluoxetine (Prozac)
Gatifloxacin (Zymar)
Ibutilide (Corvert)
Methadone
Procainamide (Pronestyl)
Quinidine
Sotalol (Betapace)
Sparfloxacin (Zagam); no longer available in the United States
Tricyclic antidepressants

Information from reference 34.

Drug Interactions

Concurrent use of psychiatric medications and some medications commonly prescribed in primary care may lead to pharmacokinetic or pharmacodynamic interactions; therefore, when possible, primary care physicians should carefully consider risks and benefits when prescribing medications that may interact with psychiatric therapies. Pharmacokinetic interactions include those that cause changes in the metabolism of either agent. Pharmacodynamic interactions occur when two medications act at the same or related target sites, leading to additive, synergistic, or antagonistic effects.

Pharmacokinetic interactions often involve alterations in medication metabolism caused by the induction or inhibition of hepatic metabolism via the cytochrome P450 (CYP) enzyme system. Second-generation antipsychotics have varying effects on this enzyme system. Clozapine and olanzapine are primarily metabolized by the CYP1A2 system; risperidone, quetiapine, and ziprasidone by CYP3A4; and aripiprazole by CYP3A4 and CYP2D6.[37] Medications that inhibit the metabolism of second-generation antipsychotics lead to higher drug levels and may cause toxicity or increased adverse effects. Interactions that induce the metabolism of second-generation antipsychotics may lead to lower drug levels, treatment failure, increased medication doses, and the potential for increased adverse effects when the interacting drug is discontinued. *Table 5* presents selected pharmacokinetic interactions between second-generation antipsychotics and common agents.[16,37-43]

Family physicians should also be aware of pharmacodynamic interactions that may intensify the adverse effects of second-generation antipsychotics. As previously described, the concurrent use of medications that can cause QT prolongation, particularly with ziprasidone, can increase the risk of clinically significant QT prolongation and potentially increase the risk of torsades de pointes. Because of effects on alpha receptors, second-generation antipsychotics can cause orthostatic hypotension, which may intensify the effects of antihypertensive agents.

Table 5. Selected Pharmacokinetic Interactions Between Second-Generation Antipsychotics and Common Agents

Second-generation antipsychotic	*Agents that lead to increased antipsychotic drug levels*	*Agents that lead to decreased antipsychotic drug levels*
Aripiprazole (Abilify)	Clarithromycin (Biaxin)* Erythromycin* Grapefruit juice* Itraconazole (Sporanox)† Ketoconazole (Nizoral)† Quinidine†	Barbiturates Carbamazepine (Tegretol) Phenytoin (Dilantin)
Clozapine (Clozaril)	Caffeine Cimetidine (Tagamet) Ciprofloxacin (Cipro) Citalopram (Celexa) Erythromycin Fluoxetine (Prozac) Fluvoxamine (Luvox) Grapefruit juice Paroxetine (Paxil) Sertraline (Zoloft)	Barbiturates Carbamazepine Nicotine Phenytoin Rifampin (Rifadin)
Olanzapine (Zyprexa)	Ciprofloxacin Fluvoxamine	Carbamazepine Nicotine Omeprazole (Prilosec) Phenytoin Rifampin
Quetiapine (Seroquel)	Clarithromycin Erythromycin Fluconazole (Diflucan) Grapefruit juice Itraconazole Ketoconazole	Barbiturates Carbamazepine Phenytoin Rifampin Theophylline
Risperidone (Risperdal)	Clozapine Fluoxetine Paroxetine	Barbiturates Carbamazepine Phenytoin Rifampin
Ziprasidone (Geodon)	Clarithromycin Erythromycin Fluconazole Grapefruit juice Itraconazole Ketoconazole	Carbamazepine Phenytoin

**—Monitor for toxicity.*
†—Decrease aripiprazole dose by one half.
References 16 and 37 through 43.

Alcohol and agents associated with central nervous system depression (e.g., sedatives, clonidine [Catapres], antihistamines, antiemetics) may have additive effects in patients using second-generation antipsychotics. Olanzapine, quetiapine, risperidone, and ziprasidone may antagonize the effects of levodopa and dopamine agonists, potentially decreasing the therapeutic benefit of the dopamine agents.

Clozapine should not be used with other agents that increase the risk of agranulocytosis or bone marrow suppression, including carbamazepine (Tegretol), ticlopidine (Ticlid), hydroxychloroquine (Plaquenil), and propylthiouracil. Clozapine can cause additive effects when administered with other drugs that have anticholinergic effects. Aripiprazole is the antipsychotic that binds most tightly to dopamine D_2 receptors and has the potential to displace other first- and second-generation antipsychotics from their binding sites; this could lead to worsening disease symptoms when administered with other antipsychotics.[38]

Guidelines for Coordinating Patient Care

Fragmentation of care is a problem for many patients with serious mental illness, and several models address this issue.[44,45] APA practice guidelines indicate that monitoring for metabolic effects of medications is the responsibility of the prescribing physician.[46] Canadian guidelines recommend that psychiatrists perform screening tests for metabolic problems and refer patients to primary care physicians to follow up on abnormal test results.[47] Responsibility for monitoring metabolic problems and vigilance for drug interactions and adverse reactions should be shared by all prescribers.

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