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**Educational Objectives**
After studying the Academic Highlights, the participant will be able to:

- Describe primary care populations in whom treatment with atypical antipsychotics would be appropriate.

This pretest is designed to facilitate your study of the material.

1. **In the United States, atypical antipsychotics are used in primary care mainly to treat schizophrenia.**
   a. True
   b. False

*Pretest answers and Posttest on page 242.*


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CME

## ACADEMIC HIGHLIGHTS

# Using Atypical Antipsychotics in Primary Care

*This ACADEMIC HIGHLIGHTS section of* The Primary Care Companion to The Journal of Clinical Psychiatry *presents the highlights of the planning roundtable "Using Atypical Antipsychotics in Primary Care," held June 3–4, 2002, in Washington, D.C. The planning roundtable and this ACADEMIC HIGHLIGHTS were supported by an unrestricted educational grant from Janssen Pharmaceutica, L.P.*

*The planning roundtable was chaired by* ***Joseph A. Lieberman III****, M.D., M.P.H., Jefferson Medical College, Hockessin, Del. The faculty members were* ***Sally Berry****, M.D., Ph.D., Janssen Pharmaceutica, Titusville, N.J.;* ***Larry Culpepper****, M.D., M.P.H. Boston Medical Center, Mass.;* ***Robert L. Findling****, M.D., University Hospitals of Cleveland, Case Western Reserve University, Ohio;* ***Stephen R. Marder****, M.D., West Los Angeles VA Medical Center, Calif.;* ***Del Miller****, Pharm.D., M.D., University of Iowa, Iowa City;* ***Jacobo E. Mintzer****, Medical University of South Carolina, Charleston;* ***Bruce L. Saltz****, M.D., Saltz and Steinberg, M.D.P.A., Boca Raton, Fla.;* ***Zafar A. Sharif****, M.D., Creedmoor Psychiatry Institute, Queens Village, N.Y.;* ***Stephen M. Stahl****, M.D., Ph.D., Neuroscience Education Institute, Carlsbad, Calif.*

*The faculty disclosures appear at the end of this activity.*

*The opinions expressed herein are those of the authors and do not necessarily reflect the views of the CME provider and publisher or the commercial supporter.*

## The Use of Antipsychotics in Primary Care

Joseph A. Lieberman III, M.D., M.P.H, noted that primary care physicians write about 20% of the antipsychotic prescriptions filled in pharmacies, and the prescription of antipsychotics by primary care physicians has increased by 18% since 1996, when the use of atypical antipsychotics became widespread.[1]

### Diagnoses Treated in Primary Care

A substantial minority of patients with schizophrenia are under the exclusive care of a primary care physician because they live in areas without access to psychiatrists, have medical illnesses that need close monitoring, or lack insurance coverage for psychiatric care.

Primary care physicians also use antipsychotics to treat, for example, behavioral problems of dementia, bipolar disorder (in patients without access to psychiatrists), refractory anxiety and depression, severe sleep disturbances, and attention-deficity/hyperactivity disorder (ADHD) in children and teenagers. Doses of antipsychotic drugs vary with the disease state and patient age.

## Describing an Atypical: The Pathophysiologic Role of Serotonin (5-HT) and Dopamine ($D_2$) Receptor Binding

Stephen M. Stahl, M.D., Ph.D., described antipsychotic pathophysiology. All antipsychotic agents are $D_2$ receptor antagonists. The current theory is that conventional, or typical, antipsychotics are not only $D_2$ antagonists but tight-binding $D_2$ antagonists, so they stay bound a long time. This persevering receptor occupancy—i.e., the receptors are continuously bombarded with the drug—creates not only an antipsychotic effect but also motor side effects known as extrapyramidal symptoms (EPS).

The atypical antipsychotics block the $D_2$ receptors with more rapid dissociation (i.e., they are more loosely bound) than conventional agents, leading to fewer motor side effects.[1] Low-potency atypical agents (requiring higher milligram doses such as quetiapine and clozapine) have faster dissociation from the $D_2$ receptor than high-potency atypical agents (requiring lower milligram doses, such as risperidone), with intermediately dosed agents (like olanzapine) in the middle.

The reduced $D_2$ receptor blockade with atypical antipsychotics has been linked to their antagonism of 5-$HT_{2A}$ receptors. Antipsychotics could have atypical action due to the 5-$HT_{2A}$ antagonism superimposed on the blockade of $D_2$ binding, reducing the $D_2$ binding enough to reverse motor side effects without reversing antipsychotic effects. However, the serotonin antagonism may not be the cause of the loose $D_2$ binding. Positron emission tomography scans of patients taking antipsy-

chotics showed that when $D_2$ binding in the striatum was high, even in the presence of high 5-$HT_{2A}$ binding in the cortex, motor side effects still occurred.[2]

Knowing that selective serotonin reuptake inhibitors (SSRIs) increase serotonin, primary care physicians often ask whether, if antipsychotics block serotonin, the patient will become depressed. But the actions of antipsychotics actually enhance antidepressant action, because although antidepressants increase actions at serotonin receptors acutely, they do ultimately decrease them. Although antipsychotics are not robust monotherapies for depression, they can have a rapid augmenting effect when administered with antidepressants.

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## Safety of Atypical Antipsychotics

Zafar A. Sharif, M.D., outlined potential side effects with antipsychotics.

### Movement Disorders

Probably the most important limitation of the conventional antipsychotic drugs was tardive dyskinesia, which occurs after long-term exposure (at least 3 to 6 months) to conventional antipsychotic drugs, but is relatively rare with atypical antipsychotics. Risk factors include advanced age, the total dose and duration of drug exposure, female gender, and diabetes.[1,2]

The reversible forms of drug-induced movement disorders, which include parkinsonian symptoms (such as tremor, rigidity, and bradykinesia), acute dystonic reactions, and akathisia, are common side effects of the older conventional antipsychotic drugs but occur less frequently with the atypical antipsychotics. One of the most distressing types of EPS is akathisia, which is a feeling of restlessness and the need to move. The liability of the newer antipsychotics for acute EPS may be dose related, so it is critical to use the lowest effective doses, particularly for populations like the elderly that are at higher risk.

### Anticholinergic Effects

Central and peripheral anticholinergic effects are of most concern in elderly patients. These include cognitive impairment, interference with memory capacity, confusion, and delirium, as well as dry mouth, blurred vision, constipation, urinary hesitancy, and tachycardia. Olanzapine has in vitro anticholinergic activity, but researchers disagree as to how much anticholinergic activity is seen clinically. Except for clozapine, other atypical antipsychotic agents lack significant anticholinergic activity.

### Weight Gain and Diabetes

Weight gain often develops over time during antipsychotic treatment, but some atypical antipsychotics are associated with more weight gain than others. A review of the published short- and long-term studies[3] revealed a mean weight gain of 2.3 kg/month during olanzapine treatment, 1.8 kg/month during quetiapine treatment, and 1.0 kg/month during risperidone treatment. Most weight gain occurred during the first 12 weeks of treatment. Ziprasidone appears to have a negligible effect on weight (0.8 kg/month). Every patient starting olanzapine or clozapine treatment should be weighed at baseline and monthly throughout treatment, but especially for the first year or two when most weight gain occurs.

Some atypical antipsychotics have been associated with glucose abnormalities and increased risk of type 2 diabetes, independent of weight gain. In a study on the prevalence of new-onset diabetes in a cohort of 38,632 patients, Sernyak et al.[4] found a statistically significant increased prevalence of diabetes in patients taking clozapine, olanzapine, or quetiapine, but not risperidone. Newcomer et al.[5] reported statistically significant glucose elevations in clozapine and olanzapine patients compared with patients receiving typical antipsychotics and healthy controls. The disturbances of glucose regulation with clozapine and olanzapine were independent of adiposity.

Patients with a family history of diabetes, who are already overweight, or who are African-American, Hispanic, and Asian are at higher risk and should have blood glucose levels measured at baseline and monthly for the first 3 months of antipsychotic treatment and then every 3 months thereafter.

### Prolactin Elevation

Prolactin elevation is a phenomenon that occurs primarily with risperidone and conventional agents. Measuring prolactin levels is seldom informative because of individual variability, so clinicians should ask patients if they have gynecomastia, galactorrhea, amenorrhea, or sexual dysfunction. Antidotes include lowering the antipsychotic dose, adding a dopamine agonist like bromocriptine, or switching to another atypical agent.

### QTc Prolongation

QTc prolongation is another potential side effect. One study[6] showed that risperidone, olanzapine, and quetiapine prolonged the QT interval less than 10 milliseconds—they were essentially benign—but ziprasidone had a 10- to 15-millisecond prolongation, although no increased risk of cardiac arrhythmia or sudden death was observed in the regulatory trials for ziprasidone. QTc prolongation resulted in a black box warning for the conventional agents thioridazine and mesoridazine. Ziprasidone should be avoided in patients with heart disease, severe cardiac dysfunction, or an already prolonged QT interval or during co-administration with other drugs that prolong QT.

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## Evidence for Using Atypical Antipsychotics in Psychosis

Stephen R. Marder, M.D., addressed the efficacy of atypical antipsychotics.

In a controversial study, Geddes and collaborators[1] concluded that conventional antipsychotics should be first-line treatments except when motor side effects such as EPS are a problem. However, most patients treated with conventional agents will experience some of these adverse effects.

Other researchers have reported atypical antipsychotics to be superior to conventional agents. Leucht et al.[2] performed a meta-analysis of double-blind, placebo-controlled trials of atypical antipsychotics and haloperidol and found that risperidone, olanzapine, quetiapine, and haloperidol were superior to placebo. When the atypical agents were compared with haloperidol, risperidone and olanzapine were statistically superior to haloperidol, but the effect sizes were small.

Perhaps the most important published study[3] comparing an atypical antipsychotic with haloperidol found risperidone superior to haloperidol in preventing psychotic relapse.


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## Evidence for Using Atypical Antipsychotics as Monotherapy and Combination Treatment in Mood and Anxiety Disorders

Larry Culpepper, M.D., M.P.H., reviewed the evidence for using atypical antipsychotics in mood and anxiety disorders either alone or in combination with other agents.

### Depression

The atypical antipsychotics olanzapine and risperidone have been found useful when added to an SSRI in treatment-resistant depression. Shelton et al.[1] conducted an 8-week, double-blind trial of olanzapine in treatment-refractory depressed patients who were randomly assigned to receive either olanzapine alone, olanzapine plus fluoxetine, or fluoxetine alone. Only the combination of olanzapine and fluoxetine showed a statistically significant response on all primary outcome measures. Risperidone up to 1 mg/day was used as adjunctive therapy in an open trial of 8 patients with refractory depression who had been treated with an SSRI.[2] All patients experienced significant improvement in rating scale scores within 1 week.

### Bipolar Disorder

Small open studies, case series, and randomized blinded controlled trials in bipolar disorder show generally uniformly positive results for atypical antipsychotics, particularly in treating acute mania.

Olanzapine is approved by the U.S. Food and Drug Administration for use in acute mania; its efficacy is well-established.[3,4] Risperidone and quetiapine have also been shown to be effective in bipolar disorder.[5–7] When risperidone was added to a mood stabilizer in a double-blind, placebo-controlled study of efficacy and safety,[5] over half the patients achieved at least a much improved rating on the Clinical Global Impressions-Improvement scale as opposed to less than one third of the placebo-treated patients.

In another controlled study,[6] 30 patients with bipolar depression were randomly assigned to receive either risperidone and placebo, paroxetine and placebo, or risperidone and paroxetine for 12 weeks. On the Montgomery-Åsberg Depression Rating Scale, there was similar improvement across treatment groups, but on the Beck Depression Inventory, the effect was more sustained for the combination of the atypical and the SSRI.

Sajatovic et al.[7] reported a statistically significant improvement in 10 patients with bipolar disorder and 10 patients with schizoaffective disorder when quetiapine was added to a mood stabilizer for 12 weeks.

A recent 3-week, placebo-controlled study of risperidone monotherapy in 262 patients with mania found greater and quicker improvements in mania in the risperidone group versus the placebo group.[8]

### Posttraumatic Stress Disorder

Treatment-resistant posttraumatic stress disorder (PTSD) appears to benefit from atypical antipsychotic treatment. Risperidone was effective in a group of veterans with severe PTSD, most of whom were also taking antidepressants,[9] and olanzapine was re-

ported to be effective in an open-label study of 30 veterans.[10] However, a study[11] of olanzapine augmentation in 19 patients with PTSD who were taking an SSRI had mixed results. Although augmentation with olanzapine was significantly more effective in reducing some specific symptoms of PTSD, no significant differences were found on clinician-rated response measures.

### Obsessive-Compulsive Disorder

Evidence also supports the use of atypical antipsychotics for obsessive-compulsive disorder (OCD). Six of 9 patients who were SSRI-resistant after 12 weeks of maximum doses showed statistically significant improvement on Yale-Brown Obsessive Compulsive Scale (YBOCS) scores within the first few weeks of olanzapine augmentation.[12] In an open-label study of 27 patients with refractory OCD who were taking maximum doses of SSRIs for 3 months, 9 of 14 patients who had quetiapine added responded with a greater than 60% improvement on the YBOCS.[13] McDougle et al.[14] studied 36 patients who had less than 35% improvement on the YBOCS after 12 weeks of SSRI monotherapy. They randomly assigned patients to either risperidone and an SSRI or an SSRI and placebo. Nine (50%) of 18 patients taking the combination responded, while the placebo group had no responders.

Another study[15] combining an SSRI with an atypical antipsychotic reported different results. Forty-four subjects nonresponsive or partially responsive to fluoxetine were given olanzapine or placebo; no significant differences in efficacy were noted during the 6-week trial.

### Tourette's Disorder

Budman et al.[16] used olanzapine in 10 adult patients with Tourette's disorder for 8 weeks. Six of 8 patients who completed the study had at least a 10-point drop on the Tourette's Symptom Severity Scale.

In a 12-week multicenter comparison of risperidone and pimozide for Tourette's syndrome,[17] both groups experienced improvement in tics, but OCD behavior improved in the risperidone group only, and fewer patients in the risperidone group reported EPS.

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## Treatment of Aggression and Agitation in Children and Adolescents

Robert L. Findling, M.D., stated that youths with aggressive behavior are not appropriate candidates for pharmacotherapy unless the behavior is persistent, pervasive, and pernicious, since nonpathologic or nonsyndromal conditions often cause youngsters to be aggressive.

Atypical antipsychotic treatment may be of benefit for a small number of children and a slightly higher number of teenagers who have conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified as primary diagnoses. Chronic pernicious aggression in these youths causes difficulty for the adults with whom they interact, their peers, and the youths themselves. Without treatment, these youths are at risk for academic underachievement, unemployment, alcohol abuse, criminality, and family, peer, and marital dysfunction.

Atypical antipsychotics including risperidone, olanzapine, and quetiapine may prove useful for pernicious, persistent aggression in children and adolescents. In addition, data are emerging about the use of these agents for psychotic, mood, and pervasive developmental disorders, as well as tics.[1]

Because risperidone was the earliest first-line atypical antipsychotic to reach the market, more is known about this agent than the other atypical antipsychotics. Findling and colleagues[2] found

very low doses of risperidone to be well tolerated and more effective than placebo in a group of children with conduct disorder. Aman and colleagues[3] reported that a mean dose of 1.2 mg/day of risperidone was significantly superior to placebo in a group of 120 children with substantial aggressive behavior, low intelligence, and a primary diagnosis within the disruptive behavior disorder spectrum.

Youths are at higher risk than adults for many of the adverse events associated with antipsychotic treatment. The younger the patient, the higher the risk of EPS, which can affect long-term adherence as well as the therapeutic alliance. Sedation can also be a problem in young people. Long-term risks include tardive dyskinesia and weight gain, which appears to be more substantial with olanzapine than risperidone. To manage weight, physicians should use the lowest dose possible along with anticipatory guidance. A percentage of young people will, despite the best of efforts, gain a marked amount of weight, and for those people, the treatment should be changed.

In adolescents with schizophrenia, the final antipsychotic doses used for optimal effectiveness are similar to those in adults. However, to avoid side effects, the dose should be titrated more slowly than with adults. Childhood schizophrenia, which is extremely rare, requires lower doses. Also, patients generally benefit from lower doses—one third to two thirds of the dose used in schizophrenia—of these agents when they are used for conditions other than schizophrenia.

Although many youths with attention-deficit/hyperactivity disorder (ADHD) have aggressive behavior, the pharmacotherapy of ADHD should focus on the core symptom cluster—restlessness, distractibility, and impulsivity. Youths who have comorbid conduct disorder or substantial difficulties with aggression experience clinically significant diminutions in aggressive behavior with methylphenidate treatment, but normalization frequently does not occur in those who have profound difficulties with aggression.

Clinicians have always had appropriate concern about overmedicating youth, but a growing body of evidence in some pediatric neuropsychiatric conditions suggests that combination pharmacotherapy may be rational, certainly for psychiatrists faced with very difficult youngsters who have aggression and comorbid ADHD. If clinicians use an atypical antipsychotic and a psychostimulant for the separate target symptoms, it is possible that lower doses of each drug can be used. The combination of a psychostimulant and atypical antipsychotic in this population appears to be safe but requires further study.

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## Managing Behavioral Dyscontrol Related to Dementia

Jacobo E. Mintzer, M.D., who outlined strategies for managing behavioral dyscontrol related to dementia, explained that dementia causes a lack of ability to express one's needs, which creates a series of behavioral disturbances. Symptoms of behavioral dyscontrol, including psychosis, agitation/aggression, anxiety, depression, apathy, and sleep disturbances, are a common reason for nursing home placement.

Evidence points to a relationship between serotonin and aggression[1] and also suggests that patients with Alzheimer's disease have a serotonin deficit.[2] Thus, agents that target both serotonin and dopamine receptors may be useful for controlling these behaviors.

Mintzer and colleagues[3] conducted a fenfluramine challenge test to study patients with dementia and aggression versus those without aggression. A hyperactive response was directly correlated with a history of aggressive behavior prior to the development of dementia. Atypical antipsychotics, which work at low doses and involve the dopamine and the serotonin system, are effective both for psychosis and aggression in these patients.

Low doses of atypical antipsychotics (1 mg/day of risperidone and 5 to 10 mg/day of olanzapine) should be tried first for dementia. Katz et al.[4] found that 1 and 2 mg/day of risperidone were superior to placebo in controlling behavioral dyscontrol, including aggression in 625 patients, mostly suffering from Alzheimer's disease, but that EPS, somnolence, falls, and urinary tract infections escalated at 2 mg/day. Street et al.[5] found that 5 and 10 mg/day of olanzapine were superior to placebo for agitation and aggression in 206 patients. Somnolence was in inverse correlation, however, with the efficacy of the dose. Little is known about quetiapine and ziprasidone in dementia.

Mood stabilizers and cholinesterase inhibitors may also be useful in this population for controlling the behavioral symptoms of dementia.

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## Pharmacokinetics and Drug-Drug Interactions of Atypical Antipsychotics and Dosing in Special Populations

Zafar A. Sharif, M.D., described atypical antipsychotic pharmacokinetics, drug-drug interactions, and dosing in special populations.

Variations in steady state plasma half-lives for atypical antipsychotics affect dosing. Clozapine (4- to 12-hour half-life), quetiapine (3- to 4-hour half-life) and ziprasidone (6-hour half-life) need b.i.d. dosing, while olanzapine (30-hour half-life) and risperidone (4- to 6-hour half-life for the parent compound and 20- to 24-hour half-life for the active metabolite) are dosed once daily. Drugs take about 5 half-life durations to reach steady state in plasma, so olanzapine and risperidone take almost a week to reach steady state, while clozapine, quetiapine, and ziprasidone should reach steady state in 1 or 2 days after a dose increase.

The cytochrome P450 (CYP) system of enzymes is the primary system involved in drug metabolism. Clozapine is metabolized by CYP 1A2, 2D6, and 3A4 enzymes. Risperidone is metabolized by the CYP 2D6 enzyme. Olanzapine has multiple pathways through CYP 1A2, 2D6, and drug glucuronidation. Quetiapine and ziprasidone are fairly limited to the CYP 3A4 isoenzyme system.

Drug-drug interactions may result from either inhibiting the enzymes that metabolize the drug or from inducing the enzymes, making them more efficient at metabolizing the drug. Additionally, younger people metabolize faster than older people, and men metabolize faster than women. Ziprasidone seems to be the only drug whose absorption is improved by the presence of food.

Inhibitors of 1A2 (fluvoxamine), 2D6 (fluoxetine, paroxetine, and high-dose sertraline), or 3A4 (erythromycin, some antifungal drugs, and protease inhibitors) enzymes potentially raise the plasma level of clozapine such that dose reduction may be necessary. Dramatic increases in blood drug level could increase dose-related side effects such as seizure or sedation. A major inducer of 1A2, which may lower blood clozapine and olanzapine levels, is cigarette smoking, and 80% to 90% of patients with schizophrenia smoke. Thus, a higher dose may be needed for a heavy smoker to maintain the same plasma level as a nonsmoker. Inducers of 3A4—barbiturates, phenytoin, carbamazepine, glucocorticoids—can also lower the level of clozapine, requiring a dose increase.

Olanzapine is similar to clozapine, but dose adjustment is usually only necessary when several factors affecting metabolism co-exist. In a young male smoker, 20 mg/day or higher is probably needed, but in an elderly female nonsmoker, 5 mg/day might suffice.

The 2D6 enzyme converts risperidone to 9-hydroxy risperidone. In normal metabolizers (90% to 95% of the population), the predominant active moiety is 9-hydroxy risperidone. In slow metabolizers, the predominant active moiety is risperidone. Paroxetine and fluoxetine are potent inhibitors of the 2D6 isoenzyme system and essentially convert a normal metabolizer to a slow metabolizer.

Quetiapine and ziprasidone are similarly metabolized almost exclusively through 3A4 isoenzymes, so erythromycin, ketoconazole, or protease inhibitors could raise the level of the drug, requiring a dose reduction due to sedation and orthostasis. Orthostasis will generally not occur at steady state, except in some elderly patients. The drug may lose effectiveness if given with 3A4 enzyme inducers—phenytoin, carbamazepine, barbiturates, rifampin, and glucocorticoids.

In elderly patients with dementia, start risperidone at a low dose (0.25 or 0.5 mg/day). This targets psychotic symptoms and behavioral disturbances. The dose can be gradually increased to 1.5 mg/day. Higher doses increase the risk of EPS. Initially start b.i.d. dosing, and then switch to a single nighttime dose. In the same population, the target dose of olanzapine should be 5 to 10 mg daily. Quetiapine should be started at 25 mg/day. Gradual titration is important to avoid sedation and orthostasis. The target dose of neither quetiapine nor ziprasidone is well defined.

In elderly patients with schizophrenia, the dose is higher than the dose in patients with dementia: 2 to 3 mg/day of risperidone, 10 to 15 mg/day for olanzapine, and 200 to 300 mg/day of quetiapine.

For bipolar disorder in elderly patients, the probable dose ranges are 1 to 3 mg/day of risperidone and 10 to 15 mg/day of olanzapine; there are no clear data for quetiapine or ziprasidone.

## Sedation Versus Sleep Versus Efficacy

Del Miller, Pharm.D., M.D., noted that sedation, a common side effect of antipsychotic medications, can be beneficial or detrimental. Individuals with schizophrenia, bipolar illness, depression, and dementia often suffer from insomnia. Patients with schizophrenia tend to have prolongation of sleep latency, shortening of total sleep time, increased periods of wakefulness after sleep onset, and decreased sleep efficiency.[1] Sedative antipsychotics can promote sleep in individuals with insomnia and help in the treatment of acutely agitated patients.

On the other hand, some patients with schizophrenia and depression sleep excessively and others have comorbid sleep apnea. Sedation can impair a person's ability to return to school or work, socialize normally, and benefit from psychosocial training or psychiatric rehabilitation. In the elderly, sedation tends to persist, impair arousal levels during the day, and lead to increased risk of falls.

Antipsychotics vary in their ability to block the histamine $H_1$ receptors that affect sedation, and sedation often appears to be dose related. Jibson and Tandon,[2] who compared sedation with various antipsychotics suggested that of the newer antipsychotics, clozapine

caused the greatest amount of sedation, followed by olanzapine and quetiapine; risperidone and ziprasidone caused the least amount of sedation.

To manage patients with persistent sedation who are taking antipsychotics, the 1999 Schizophrenia Expert Consensus Guidelines[3] suggest first eliminating any other sedating agents, including antidepressants such as the tricyclics and mirtazapine as well as mood-stabilizing drugs like valproic acid. Bedtime dosing may decrease daytime sedation. Clinicians can consider reducing the dose of the antipsychotic slowly or switching to a less sedating antipsychotic. Hypothyroidism should also be ruled out as a cause of sedation. Caffeine and bupropion may be useful for some patients. Stimulants are not recommended to treat sedation.

To manage patients with chronic insomnia, the same guidelines[3] recommend switching to a more sedating antipsychotic—olanzapine, clozapine, or quetiapine. Sedation alone is not a reason to switch to clozapine. Other sedatives could be added, such as benzodiazepines, trazodone, zolpidem, antihistamines, or chloral hydrate.

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## Metabolic Changes Associated With Antipsychotic Use

Joseph A. Lieberman III, M.D., led a discussion on metabolic changes associated with antipsychotic use. Against the background of an epidemic of obesity in the United States, some antipsychotics are associated with weight gain, hyperglycemia, the onset of type II diabetes, and diabetic ketoacidosis.

Psychotic patients often have poor glycemic control, exercise habits, and diet, so inadequate treatment of psychosis in patients with diabetes leads to adverse medical consequences. A patient with metabolic risks might need an antipsychotic dosage adjustment or the addition of a lipid-lowering medication, which is usually well tolerated. Achieving improvement in psychiatric symptoms may allow patients to pursue weight loss and exercise.

When a patient enters a primary care office, blood pressure, weight, temperature, and pulse rate are typically measured, and an assessment of pain is conducted. A dramatic weight gain should trigger a red flag. Screening for hyperlipidemia and hyperglycemia is also becoming routine in primary care because of the emergence of the epidemic of diabetes in this country.

Primary care physicians are usually better equipped than psychiatrists to monitor weight gain and diabetic signals, since the average private psychiatric practice has no exam room or laboratory.

Using cautious doses of atypical antipsychotics may lessen adverse events. A dose response for weight gain has not been established, but the development of hyperglycemia and diabetic ketoacidosis is most likely to occur at either initiation of therapy with the atypical antipsychotic or with an increase in dose. So a patient who has been treated for several months without metabolic issues should have more vigilant monitoring at the time the dose is increased.

When starting an antipsychotic, educate the patient and family members that weight gain is a possibility and suggest monitoring for signs of weight gain, e.g., tight clothes. The physician should also weigh patients at every visit and give them nutritional consultation.

Some patients may resist using a drug associated with weight gain but will be reassured if they are told the usual weight gain is about 5 lb (2.25 kg). Patients would rather be warned in advance than surprised after several weeks of treatment. It is important that they feel they can bring up their concerns to the physician, and that if weight gain is bothersome, the treatment can be changed. But they should be reminded that weight gain is reversible, whereas the consequences of an untreated psychiatric disorder may be severe.

## Recognizing Movement Disorders in the Elderly

Bruce L. Saltz, M.D., stated that recognition and management of drug side effects in the elderly are just as important as recognition and management of dementia. Drug-induced movement disorders develop more readily and are more persistent in the elderly than in younger patients. Extrapyramidal dysfunction—parkinsonism, akathisia, dystonia, or choreiform-type dyskinesia—is extremely prevalent in institutionalized elderly who take conventional antipsychotics. In neuroleptic-naïve younger patients, the 1-year reported incidence rate of tardive dyskinesia is approximately 5%, while the 1-year incidence in older adults is 25% with conventional antipsychotics.[1] The dyskinesias that older adults experience tend to be more persistent and can lead to more dysfunction such as problems with eating and ambulation. In the upper extremities, finger movements are the most common tardive dyskinesia movement. In the lower extremities, common tardive dyskinesia movements include movements of the toes, ankles, or legs at the knees or hips.

Educational programs on movement disorders are needed for primary care physicians, nurses, psychologists, social workers, and even patients and caregivers. These programs must be brief, interesting, and effective. One of the best methods for learning about presentations of movement disorders is by video. Educational video clips can show the signs and symptoms that should be noticed, such as problems with ambulation, tremor, postural stability, and involuntary spasms.

Examination for abnormal movements should begin by having the

seated patient relax and look straight forward. Shoes and socks should be removed. Facial grimacing or tics, forced eye closure, and lip or tongue movements may be revealed. Sometimes these movements and many others may be seen when patients are distracted or activated by provocation procedures. For example, while the patient's mouth is open for 20 to 30 seconds, ask the patient to extend one arm while tapping each finger to the thumb or open and close the hand; orofacial movements may be noticed. Other techniques may elicit movements in other body regions.

### REFERENCE

1. Woerner MG, Alvir JM, Saltz BL, et al. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998;155:1521–1528

## Prolactin Changes Associated With Antipsychotic Use

Sally Berry, M.D., Ph.D., addressed hyperprolactinemia. Prolactin is a hormone secreted from the pituitary into the blood, and its major function is to support lactation in women. Dopamine has an important role in the regulation of prolactin release. The tuberoinfundibular dopamine neuron pathway in the hypothalamus controls the release of prolactin. Dopamine is released from the tuberoinfundibular dopamine neurons into the hypophyseal portal system wherein dopamine acts as a neurohormone rather than a neurotransmitter—the effect is to reduce the release of prolactin.

Antipsychotics available today are dopamine antagonists. If dopamine suppresses the release of prolactin, one would expect the blockade of dopamine receptors to result in an increase in serum prolactin levels. This mode of dopamine dysregulation is called drug-induced hyperprolactinemia.

However, not all antipsychotics are associated with hyperprolactinemia. Clozapine, for example, does not cause hyperprolactinemia. A nonclinically significant, and often transitory, increase in serum prolactin may occur during treatment with olanzapine, quetiapine or ziprasidone, while risperidone-treated patients may experience prolactin increases that persist throughout treatment but are usually asymptomatic.

Galactorrhea, gynecomastia, amenorrhea, and sexual dysfunction are clinical signs possibly related to hyperprolactinemia. Gynecomastia—increase in breast tissue—can be cosmetically troubling to men, and the infertility that results from lack of menstruation could be problematic in antipsychotic-treated women of childbearing age. Sexual dysfunction common in schizophrenia includes erectile dysfunction, reduced libido, and anorgasmia. Berry and colleagues[1] found that prolactin elevation was not correlated with common sexual symptoms in schizophrenic patients, including sexual dysfunction in men and menstrual changes in women, but was associated with reduction of positive symptoms and anxiety/depression symptoms.

When starting a patient, especially a young man, on antipsychotic therapy, it helps to tell him matter-of-factly that there are side effects associated with all drugs, and these drugs in particular can affect sexual functioning, making it difficult to get or maintain an erection. If that should happen, he should contact the physician and not just stop the medication.

Physicians can assume that a patient taking a conventional antipsychotic or risperidone has hyperprolactinemia, but routinely measuring levels before and during therapy is unnecessary. At each visit, patients should be queried about troublesome symptoms that may possibly be related to hyperprolactinemia. The first step after the emergence of symptoms is to reduce the dose of the antipsychotic. If the symptoms persist, measure the prolactin levels. Then, if the prolactin level is greater than 100 μg/L, talk to an endocrinologist about ruling out pituitary adenomas and microadenomas. An alternative is to switch to an antipsychotic that is not associated with hyperprolactinemia, considering the rest of the drug's side effect profile for that particular patient.

If there are reasons to stay with the original antipsychotic, adding a dopamine agonist is an option. When the patient has an underlying psychotic illness, there is a risk associated with dopamine agonists of causing an exacerbation or reemergence of the underlying psychosis. Physicians may wish to partner with an endocrinologist regarding dopamine agonist treatment.

### REFERENCE

1. Berry SA, Martinez RA, Gudelsky GA, et al. Serum prolactin in schizophrenia. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico

## Managing Anticholinergic Side Effects

Joseph A. Lieberman III, M.D., noted that the nature of anticholinergic side effects can be peripheral or central. Peripheral side effects include dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate, and decreased sweating. Central effects include cerebration, impaired concentration or confusion, attention deficits, and memory impairment. Central side effects must be differentiated from those caused by the patient's psychosis.

These effects may lead to unwanted complications. Decreased salivation can lead to dental caries, ulceration of the gums, and buccal mucosa. Decreased bronchial secretions can lead to mucous plugging of small airways

in patients with asthma and bronchitis. Decreased sweating can lead to hyperthermia, which is particularly a problem in elderly patients who already have some dysregulation of temperature control. Increasing pupil size can lead to photophobia and precipitation of acute narrow angle glaucoma with blurred vision, especially when reading small print. Increased heart rate can lead to angina and even, in extreme cases, to myocardial infarction. Difficulty urinating can lead to bladder distension and, in extreme cases, urinary retention. And constipation and bowel obstruction can lead to life-threatening problems.

So the potential medical complications of the anticholinergic side effects are appreciable, and in susceptible patients, particularly older patients or patients with a preexisting conditions, these effects can be debilitating.

A general approach to managing anticholinergic side effects is to decrease the dose of the antipsychotic if the therapeutic effect can be maintained. If not, change to an antipsychotic with a lesser anticholinergic profile. Some data demonstrate in vitro differences; whether they translate to clinical activity is subject to debate. Also, eliminate or lower doses of other agents the patient is taking that are known to produce anticholinergic side effects. Some elderly patients are taking over a dozen medications; determine how many of these are really necessary.

Keep in mind specific situations. Narrow angle glaucoma is an absolute contraindication to use of antipsychotics unless the glaucoma is properly treated. Prostatic hypertrophy is a relative contraindication. Bethanechol can be used on occasion throughout the course of therapy for these patients to offset the obstruction.

Anticholinergic delirium constitutes a medical emergency. The symptoms are hot dry skin, dry mucous membranes, dilated pupils, absent bowel sounds, and tachycardia. Physostigmine will help but cannot be used to sustain reversal of symptoms because it runs the risk of a cholinergic crisis. Those symptoms are nausea, vomiting, bradycardia, and seizures, and the treatment is atropine.

***Faculty Disclosures***

*In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this educational activity were asked to complete a full disclosure statement. The information received is as follows:* **Dr. Lieberman** *is a consultant for Abbott, Bristol-Myers Squibb, Forest, Janssen, Pfizer, Novo Nordisk, and Sanofi-Synthelabo;* **Dr. Berry** *is an employee of Janssen;* **Dr. Culpepper** *is a consultant for, has received honoraria from, and is on the speakers/advisory boards for Abbott, Forest, Janssen, Lilly, Pfizer, and Wyeth;* **Dr. Findling** *is a consultant for, has received grant/research support and honoraria from, and is on the speakers/advisory boards for Janssen, Bristol-Myers Squibb, Lilly, AstraZeneca, Pfizer, and Novartis;* **Dr. Marder** *is a consultant for, has received grant/research support and honoraria from, and is on the speakers/advisory boards for Janssen, Lilly, Bristol-Myers Squibb, AstraZeneca, and Pfizer;* **Dr. Miller** *has received grant/research support from and is on the speakers/advisory boards for Janssen and Bristol-Myers Squibb, and has received honoraria from Janssen, Bristol-Myers Squibb, and Pfizer;* **Dr. Mintzer** *is a consultant for Lilly, Abbott, AstraZeneca, Bristol-Myers Squibb, Capital Research Company, and The Council on Healthcare Advisors, has received grant/research support from Abbott, Alzheimer's Disease Cooperative Study, AstraZeneca, Bristol-Myers Squibb, Eisai Inc., Forest, Fujisawa Institute of America, Lilly, Janssen, Johnson & Johnson, National Institute on Aging, Novartis, Parke-Davis, Pfizer, Sanofi-Synthelabo, Somerset, SmithKline, and Wyeth, and is a member of the speakers bureau for Abbott, AstraZeneca, Eisai, Lilly, Janssen, and Pfizer;* **Dr. Saltz** *has received grant/research support from the National Institute on Aging and the National Institutes of Health;* **Dr. Sharif** *has received grant/research support from Janssen and is on the speakers/advisory board for Bristol-Myers Squibb and Janssen;* **Dr. Stahl** *is a consultant for, has received research/grant support from, and is on the speakers/advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Forest, GlaxoSmithKline, Janssen, Lundbeck, Organon, Parke-Davis, Pfizer, Pharmacia, Sanofi-Synthelabo, Solvay, Watson, Wyeth, Yamanouchi, Abbott, Aventis, Fabre Kramer, Lorex, Neurocrine, Novartis, Pierre Fabre, Roche, Sanao, Searle, and Sumitomo.*

***Disclosure of off-label usage***

*The chair of this activity has determined that, to the best of his knowledge, olanzapine is not approved by the U.S. Food and Drug Administration for the treatment of depression, anxiety (including obsessive-compulsive disorder and posttraumatic stress disorder), dementia, and childhood conduct disorder; pimozide is not approved for the treatment of Tourette's disorder; quetiapine is not approved for anxiety, depression, or bipolar disorder; and risperidone is not approved for bipolar disorder, depression, anxiety (including OCD and PTSD), dementia, and childhood conduct disorder.*

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1. **The low propensity of the atypical antipsychotics to cause extrapyramidal symptoms is attributed to:**
   a. Loose binding with the $D_2$ receptors
   b. 5-$HT_{2A}$ antagonism
   c. Tight binding with $D_2$ receptors
   d. 5-$HT_{2A}$ agonism

2. **According to this report, there is evidence for using atypical antipsychotics in:**
   a. Bipolar disorder, eating disorders, and Tourette's disorder
   b. Depression, obsessive-compulsive disorder, and substance abuse
   c. Posttraumatic stress disorder, obsessive-compulsive disorder, and bipolar disorder
   d. Obsessive-compulsive disorder, bipolar disorder, eating disorders

3. **According to this report, which of the following conditions in children may be treated with an atypical antipsychotic?**
   a. ADHD and impulsivity
   b. Treatment-resistant depression
   c. Comorbid bipolar disorder and ADHD
   d. Conduct disorder with chronic pernicious aggression

4. **According to this report, one of the leading reasons for nursing home placement of people with dementia is:**
   a. Inability to prepare meals
   b. Behavioral symptoms including psychosis, agitation, and sleep disturbances
   c. Comorbid medical illness such as cancer or emphysema
   d. Lack of interest in family members

5. **According to this report, drug-induced hyperprolactinemia should be managed by:**
   a. Routinely measuring prolactin levels at baseline and every 3 months thereafter
   b. Routinely measuring prolactin levels after 6 months of treatment
   c. Educating patients about the side effects of hyperprolactinemia and questioning them about these side effects at visits
   d. Waiting for patients to report the side effects of hyperprolactinemia

**Answers to Pretest: 1. b**

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