Adverse Effects of Antipsychotic Medications

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The use of antipsychotic medications entails a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of troubling, sometimes life-shortening adverse effects. There is more variability among specific antipsychotic medications than there is between the first- and second-generation antipsychotic classes. The newer second-generation antipsychotics, especially clozapine and olanzapine, generally tend to cause more problems relating to metabolic syndrome, such as obesity and type 2 diabetes mellitus. Also, as a class, the older first-generation antipsychotics are more likely to be associated with movement disorders, but this is primarily true of medications that bind tightly to dopaminergic neuroreceptors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. Anticholinergic effects are especially prominent with weaker-binding first-generation antipsychotics, as well as with the second-generation antipsychotic clozapine. All antipsychotic medications are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, cardiac arrhythmia, and sudden cardiac death. Primary care physicians should understand the individual adverse effect profiles of these medications. They should be vigilant for the occurrence of adverse effects, be willing to adjust or change medications as needed (or work with psychiatric colleagues to do so), and be prepared to treat any resulting medical sequelae. (*Am Fam Physician*. 2010;81(5):617-622. Copyright © 2010 American Academy of Family Physicians.)

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Antipsychotic medications effectively diminish the intensity of psychotic hallucinations, allowing most institutionalized patients with schizophrenia to be discharged into community treatment. The first-generation antipsychotics (FGAs) work through dopamine D_2 neuroreceptor blockade, and a subsequent series of new antipsychotics were developed with stronger dopamine blockade.[1] To discuss differences in the adverse effect profiles of FGAs, we use the terms "low-potency" and "high-potency," not to indicate their clinical effectiveness, but rather to indicate their potency in binding to this dopamine D_2 neuroreceptor. *Table 1* outlines selected FGAs, the usual maintenance dosage, and relative potency of dopamine D_2 neuroreceptor blockade.

Table 1. Selected Conventional or First-Generation Antipsychotics

Drug	*Usual daily maintenance dosage*	*Dopamine D_2 neuroreceptor potency*
Chlorpromazine	400 mg	Low
Thioridazine	200 to 300 mg	Low
Perphenazine	24 mg	Medium
Fluphenazine	10 to 20 mg	High
Haloperidol (formerly Haldol)	10 to 15 mg	High
Thiothixene (Navane)	30 mg	High
Trifluoperazine	20 mg	High

Second-generation antipsychotics (SGAs) were launched in 1989 when investigators found that clozapine (Clozaril) was more effective than chlorpromazine, with fewer extrapyramidal symptoms.[2] These new antipsychotics were considered atypical because they targeted neuroreceptors other than only dopamine. Over the past two decades, SGAs have dominated prescribing preferences in the United States under the assumption that they are more effective and safer than FGAs.[3] *Table 2* lists SGAs marketed in the United States, the year in which each was introduced, and the usual daily dosage.

The results of two recent publicly funded studies designed to evaluate the effectiveness of these treatments under real-world conditions have called into question these prescribing preferences. The Clinical Antipsychotic Trials of Intervention Effectiveness study was designed to compare the FGA perphenazine with several SGAs, using "all-cause discontinuation" as a proxy measure for effectiveness.[4] The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
FGAs with lower potency dopamine D_2 neuroreceptor blockade (Table 1) are no more likely than most SGAs to cause extrapyramidal symptoms.	A	4, 5, 9
FGAs and the SGA risperidone (Risperdal) commonly cause hyperprolactinemia. Physicians should be vigilant for signs and symptoms of hyperprolactinemia in patients taking these medications.	C	6, 19
Patients taking SGAs, especially clozapine (Clozaril) and olanzapine (Zyprexa), should be monitored closely for weight gain and other metabolic syndrome–related adverse effects (Table 4).	C	39
Antipsychotic medications should be used with caution in older adults because of the risk of increased mortality from sudden cardiac death and cerebrovascular accidents.	A	40-42

FGAs = first-generation antipsychotics; SGAs = second-generation antipsychotics.

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, go to http://www.aafp.org/afpsort.xml.

Study measured quality of life and other effectiveness measures.[5] Neither study demonstrated a clear difference in effectiveness between FGAs and non-clozapine SGAs.

With the exception that clozapine is more effective for treatment-resistant patients,[6] the choice of antipsychotic should depend on the potential for adverse effects in individual patients. General comparisons between the FGA and SGA classes are less helpful than comparisons among specific medications because each presents its own challenges in terms of balancing effectiveness with safety and tolerability. This article reviews some of the more important adverse effects of antipsychotics, and includes a summary table of the comparative risks *(Table 3)*.[6,7]

Sedation

Sedation is common with antipsychotic medications and is dose related. It can be a cause of poor compliance and, if persistent, can interfere with social and vocational functioning. Many patients become tolerant to the sedative effect over time. Low-potency FGAs and clozapine are the most sedating, with some effect from olanzapine (Zyprexa) and quetiapine (Seroquel).[6] Somnolence can be alleviated by lowering the dosage, changing to a single bedtime dose, or switching to a less sedating medication.

Table 2. Atypical or Second-Generation Antipsychotics Marketed in the United States

Drug	*Year introduced*	*Usual daily dosage*
Aripiprazole (Abilify)	2002	10 to 30 mg
Clozapine (Clozaril)	1989	300 to 600 mg
Olanzapine (Zyprexa)	1996	10 to 20 mg
Quetiapine (Seroquel)	1998	250 to 600 mg
Risperidone (Risperdal)	1994	3 to 6 mg
Ziprasidone (Geodon)	2001	40 to 80 mg

NOTE: *Paliperidone, the active metabolite of risperidone, has been marketed in the United States as Invega since 2007. There is insufficient long-term clinical information on this medication to include it in this review. It is likely that the adverse effect profile of Invega will be similar to that of risperidone.*

Hypotension

Orthostatic hypotension can occur with all antipsychotic medications, depending on the degree of α_1-adrenoreceptor antagonism, particularly with low-potency FGAs and clozapine. It can also occur with risperidone (Risperdal) and quetiapine, especially with rapid titration. This effect is more common in older adults (with risk of falls), those on blood pressure medications, and those who have other cardiovascular diseases. With careful dose titration, patients may become tolerant to this effect. Treatment options include decreasing or dividing doses or switching to a medication with a lesser antiadrenergic effect.[6]

Anticholinergic Effects

Anticholinergic effects include constipation, urinary retention, dry mouth, blurred vision and, at times, cognitive impairment. These symptoms can lead to other problems such as tooth decay, falls, or gastrointestinal obstruction. Low-potency FGAs and clozapine are highly likely to cause anticholinergic effects; olanzapine and quetiapine have been shown to do so at high dosages.[8] When needed, doses can be lowered or divided to help alleviate this problem.

Extrapyramidal Symptoms

Antipsychotic medications cause four main extrapyramidal symptoms: pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia. The first three usually begin within a few weeks of starting a new medication (or increasing the dosage). These symptoms may cause discomfort, social stigma, and poor compliance. They are more likely to occur with higher dosages of

Table 3. Comparative Risk of Adverse Effects of Antipsychotic Medications*

Adverse effect	Low-potency FGAs†	High-potency FGAs‡	SGAs					
			Aripiprazole (Abilify)	Clozapine (Clozaril)	Olanzapine (Zyprexa)	Quetiapine (Seroquel)	Risperidone (Risperdal)	Ziprasidone (Geodon)
Anticholinergic effects	+++	+	0	+++	+	+	0	0
Dyslipidemia	++	+	0	+++	+++	++	+	0
Extrapyramidal symptoms	+	+++	+	0	+	0	++	+
Hyperprolactinemia	++	+++	0	0	+	0	+++	+
Neuroleptic malignant syndrome	+	++	+	+	+	+	+	+
Postural hypotension	+++	+	+	+++	+	++	++	+
Prolonged QT interval	++§	+	+	+	+	+	+	++
Sedation	+++	+	+	+++	++	++	+	+
Seizures	+	+	+	+++	+	+	+	+
Sexual dysfunction	+++	++	+	+	+	+	++	+
Type 2 diabetes mellitus	+	+	+	++	++	+	+	+
Weight gain	++	+	0	+++	+++	++	++	0

NOTE: *0 = rare; + = lower risk; ++ = medium risk; +++ = higher risk.*

FGAs = first-generation antipsychotics; SGAs = second-generation antipsychotics.

**—Effects are approximate, and relative to other antipsychotic medications rather than absolute risk of an adverse effect occurring.*

†—*FGAs with lower potency dopamine D_2 neuroreceptor blockade, including chlorpromazine and thioridazine.*

‡—*FGAs with higher potency dopamine D_2 neuroreceptor blockade. These include fluphenazine, haloperidol (formerly Haldol), thiothixene (Navane), and trifluoperazine. Please note that the FGA perphenazine is considered to have intermediate dopamine D_2 neuroreceptor blockade, with an adverse effect profile between the low- and high-potency FGAs.*

§—*Individually, thioridazine has a higher risk of prolonged QT interval and should be used only when no other appropriate options are available.*

Adapted with permission from Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ. *2005;172(13):1703-1711, with additional information from reference 6.*

high-potency FGAs, such as haloperidol (formerly Haldol), and are less likely with FGAs that have weaker dopamine blockade. Several meta-analyses, most comparing SGAs with haloperidol, have shown that SGAs are less likely to cause extrapyramidal symptoms.[6] However, recent studies comparing SGAs with lower potency FGAs have not shown this difference.[4,5,9]

PSEUDOPARKINSONISM

Pseudoparkinsonism is a reversible syndrome that includes tremulousness in the hands and arms, rigidity in the arms and shoulders, bradykinesia, akinesia, hypersalivation, masked facies, and shuffling gait. The presence of bradykinesia or akinesia can create a diagnostic dilemma, with symptoms resembling depression or even the negative symptoms of schizophrenia (i.e., an inability to pay attention, the loss of a sense of pleasure, the loss of will or drive, disorganization or impoverishment of thoughts and speech, flattening of affect, and social withdrawal). Treatment options include dosage reduction or the addition of oral anticholinergic agents (e.g., benztropine, diphenhydramine [Benadryl]); physicians should keep in mind that these medications can cause their own adverse effects.

AKATHISIA

Akathisia is described subjectively as a feeling of inner restlessness that can be manifested as excessive pacing or inability to remain still for any length of time. It can be difficult to differentiate akathisia from psychiatric anxiety and agitation. Treatment of akathisia can include a dosage reduction when possible, or the addition of a low-dose beta blocker, such as propranolol (Inderal) at 20 to 80 mg per day.[10]

DYSTONIC REACTIONS

Dystonic reactions are spastic contractions of the muscles, including oculogyric crisis, retrocollis, torticollis, trismus, opisthotonos, or laryngospasm. These reactions are uncomfortable and can be life threatening if left

untreated. Intervention often requires administration of intravenous or intramuscular anticholinergic agents.

TARDIVE DYSKINESIA

Tardive dyskinesia is an involuntary movement disorder that can occur with long-term antipsychotic treatment, and may not be reversible even if the medication is discontinued. Tardive dyskinesia usually involves the orofacial region, but all parts of the body can be involved. Abnormal movements can include myoclonic jerks, tics, chorea, and dystonia. They become most evident when patients are aroused, but ease during relaxation and disappear during sleep.[11] Risk factors for developing tardive dyskinesia include long-term therapy with FGAs at higher dosages, older age, female sex, and concurrent affective disorders.[6] Attempts to treat tardive dyskinesia usually begin by discontinuing the offending agent or switching to one with a lower risk, but evidence is insufficient to show that this or any other treatment markedly reduces symptoms after onset.[12-18]

Hyperprolactinemia

Antipsychotics cause high prolactin levels by blocking the normal tonic inhibition on pituitary mammotropic cells of dopamine produced in the hypothalamus. Hyperprolactinemia is common with the use of any FGA, as well as with the SGA risperidone (up to 60 percent of women and 40 percent of men),[19] and is dose dependent. It appears to be much less common with other SGAs, but has been reported with the use of olanzapine and ziprasidone (Geodon) at high dosages.[6]

Hyperprolactinemia can be asymptomatic, but may cause gynecomastia, galactorrhea, oligo- or amenorrhea, sexual dysfunction, acne, hirsutism, infertility, and loss of bone mineral density. Symptoms often appear within a few weeks of beginning the antipsychotic or increasing the dosage, but can also arise after long-term stable use.

There is growing evidence that chronic hyperprolactinemia from antipsychotics can cause osteoporosis and an increased risk of hip fracture. A recent case-control analysis of a large general practice database in the United Kingdom showed that the risk of hip fracture was 2.6 times higher in patients taking prolactin-raising antipsychotics compared with the general population.[20] Physicians should routinely inquire about symptoms that might reflect hyperprolactinemia in patients taking prolactin-raising antipsychotics and, if present, measure the serum prolactin level. Presence of osteoporosis, sexual side effects, or prolactin-dependent breast cancer may necessitate switching to an antipsychotic that does not raise prolactin levels, such as aripiprazole (Abilify) or quetiapine.[21]

Sexual Dysfunction

Up to 43 percent of patients taking antipsychotic medications report problems with sexual dysfunction, a distressing adverse effect that can lead to poor medication adherence.[22] Use of antipsychotics can affect all phases of sexual function, including libido, arousal, and orgasm. Both FGAs and SGAs can impair arousal and orgasm in men and women.[23,24] FGAs especially have been found to cause erectile and ejaculatory dysfunction in men, including spontaneous, painful, or retrograde ejaculation, as well as priapism.

Agranulocytosis

In rare cases, clozapine may cause neutropenia (absolute neutrophil count [ANC] of less than 1,500 cells per mm^3 [1.50×10^9 per L]) and agranulocytosis (ANC of less than 500 cells per mm^3 [0.50×10^9 per L]) that can lead to potentially fatal infections. Agranulocytosis occurs in slightly less than 1 percent of patients, almost always within three months of starting treatment (84 percent).[25] Risk increases with older age, female sex, and Asian race.[6] The U.S. Food and Drug Administration (FDA) requires that clozapine be available only through programs that monitor white blood cell counts weekly for the first six months, every two weeks for the next six months, and monthly thereafter. According to FDA guidelines, the medication should be stopped if the white blood cell count drops below 3,000 cells per mm^3 (3.00×10^9 per L) or the ANC level below 1,500 cells per mm^3.

Cardiac Arrhythmias

All antipsychotics can contribute to prolongation of ventricular repolarization (prolonged QT interval), which can in turn lead to torsades de pointes and sudden cardiac death. This effect is most marked with the low-potency FGA thioridazine and the SGA ziprasidone, and is dose dependent.[26] The incidence of sudden cardiac death among patients taking antipsychotics is about twice that of the general population.[27,28]

Physicians should avoid combining antipsychotic medications with other medications that prolong the corrected QT interval (e.g., classes I and III antiarrhythmic drugs, tricyclic antidepressants, some antibiotics; see http://www.arizonacert.org). Before initiating an antipsychotic medication, the risks and benefits should be carefully weighed and reviewed with patients. Physicians should be especially vigilant in assessing potential cardiac symptoms in this population. Although it may be prudent to check baseline or posttreatment electrocardiography, especially with higher risk patients, the effectiveness of doing so has not been proven.[29]

Table 4. Monitoring Protocol for Patients on Second-Generation Antipsychotics*

Assessment parameter	*Baseline*	*4 weeks*	*8 weeks*	*12 weeks*	*Quarterly*	*Annually*	*Every 5 years*
Medical and family history, including cardiovascular disease	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

*—More frequent asssessments may be warranted based on clinical status.

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Seizures

All antipsychotics can lower the seizure threshold. They should be used with caution in patients who have a history of seizures and in those with organic brain disorders. Generally, the more sedating the antipsychotic, the more it lowers the seizure threshold. Seizures are most common with low-potency FGAs and clozapine, especially at higher dosages.[30] Depot antipsychotics should not be used in patients with epilepsy because they cannot be quickly withdrawn.

Metabolic Syndrome Issues

Weight gain is a common adverse effect of using antipsychotic medications, and can be rapid and difficult to control.[31] Weight gain does not seem to be dose dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency FGAs.[7]

Antipsychotic medications can contribute to a wide range of glycemic abnormalities, from mild insulin resistance to diabetic ketoacidosis,[32] as well as worsening of glycemic control in patients with preexisting diabetes. Although FGAs and SGAs can cause these problems, risk is variable—the greatest risk is with clozapine and olanzapine. The magnitude of risk is difficult to quantify because so many other diabetes risk factors are present in this population. Although the weight gain associated with antipsychotics clearly contributes, there appear to be other independent effects as well.[33,34]

Dyslipidemia is also associated with several antipsychotic medications, with increases noted primarily in triglyceride levels. Low-potency FGAs and the SGAs clozapine, olanzapine, and quetiapine are associated with a higher risk of hyperlipidemia.[35-38] Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine and low-potency FGAs, and lowest with aripiprazole, risperidone, ziprasidone, and high-potency FGAs. Guidelines for preventing and monitoring metabolic changes in patients taking SGAs are shown in *Table 4*.[39]

Older Patients

Antipsychotic medications have been used in older patients who have dementia-related psychosis or behavioral difficulties. In April 2005, the FDA issued a boxed warning for SGAs after a meta-analysis showed a 1.6- to 1.7-fold increase in the risk of death associated with their use in this population.[40] In June 2008, after two large cohort studies showed similar risk with FGAs, boxed warnings were added to this class as well.[41,42] The cause of this increased mortality is at least in part from sudden cardiac death, as well as cerebrovascular accidents.

Currently, there are no medications approved for the treatment of dementia-related psychosis. Before medication is prescribed, behavioral interventions should be attempted. Any use of antipsychotics for dementia-related psychosis should be preceded by a discussion with patients, families, and caregivers about the increased risk of cerebrovascular accidents and death.

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