Second-generation antipsychotic medications: Pharmacology, administration, and side effects

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INTRODUCTION

Antipsychotic medications have unique efficacy in the treatment of acute psychosis from any cause and in the management of chronic psychotic disorders such as schizophrenia. As a class, they are also effective in the treatment of acute agitation, bipolar mania, and other psychiatric conditions.

Second-generation antipsychotics (SGAs), also known as atypical antipsychotics, generally have lower risk of extrapyramidal symptoms and tardive dyskinesia compared with first-generation antipsychotics (FGAs). First- and second-generation antipsychotic drugs are more comparable in their clinical efficacy, with the exception of clozapine, an SGA with unique efficacy in treatment-resistant schizophrenia. Antipsychotic drugs differ from one another in dosing, route of administration, pharmacokinetics, side effect profile, and cost, factors that influence the selection of an antipsychotic drug for individual patients.

The pharmacology, administration, and comparative side effects of SGAs available in the United States, including clozapine, are discussed here. The pharmacology, administration, and comparative side effects of FGAs are discussed separately, as is the use of antipsychotics in the treatment of schizophrenia, bipolar disorder, and acute agitation. Guidelines for the prescribing of clozapine are also discussed separately.

- (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Assessment and emergency management of the acutely agitated or violent adult".)
- (See "Schizophrenia in adults: Guidelines for prescribing clozapine".)

PHARMACOLOGY

The mechanism of action of most first- and second-generation antipsychotics (FGAs and SGAs) appears to be postsynaptic blockade of brain dopamine D2 receptors. Of the four exceptions, aripiprazole and brexpiprazole are D2 receptor partial agonists and cariprazine is a D3-preferring D3/D2 receptor partial agonist. Several lines of evidence support the role of these receptors in the activity of antipsychotics, most notably a strong correlation between D2 receptor binding and clinical potency [1] and a consistent requirement of 65 percent D2 receptor occupancy for antipsychotic efficacy in functional imaging studies [2]. The fourth exception, pimavanserin, is a serotonin 5HT2A inverse agonist and antagonist with no dopamine D2 affinity [3,4].

Most SGAs differ from older medications pharmacologically in that serotonin 5HT2 receptor binding exceeds their affinity for dopamine D2 receptors, whereas in FGAs this is generally not the case. Largely for that reason, 5HT2 activity has been suggested as one basis for the lower overall risk of extrapyramidal symptoms (EPS) with the atypical drugs compared with FGAs [5]. Other aspects of SGA pharmacology that correlate with reduced risk of EPS include "loose" D2 receptor binding with rapid dissociation rates [6] and preferential binding of drugs to receptors in limbic and cortical brain regions rather than striatal areas [7]. None of these hypotheses has been fully confirmed, and the most important message for the clinician is that the pharmacology of these drugs is complex and likely to result in some variability of side effect risk and pharmacokinetics from patient to patient.

Other elements of SGA pharmacology vary significantly among drugs, giving each agent a unique side effect profile, dosing pattern, rate of absorption, half-life, set of drug-drug interactions, and susceptibility to changes in hepatic and renal function (table 1 and table 2). Familiarity with these properties will aid the clinician in optimizing treatment for individual patients.

Other receptor activities — Additional receptor activities with SGAs include blockade or partial agonist activity at muscarinic, alpha-adrenergic, and histaminic receptors, with resultant

anticholinergic, hypotensive, sedative, and metabolic side effects. The diversity in SGAs' affinity for these receptors leads to significant variability in the type and extent of side effects among antipsychotics. (See 'Adverse effects' below.)

Absorption and bioavailability — The rate of absorption and bioavailability of these drugs vary significantly and may be important considerations in some cases. A drug with rapid absorption is usually preferred in an urgent situation, whereas one with slower uptake may be better tolerated. Sublingual asenapine is the most rapidly absorbed, with a one-hour time to peak serum concentration, followed closely by lurasidone and the immediate-release formulation of quetiapine [8-11]. The longest times to peak concentration are noted with olanzapine, the extended-release (XR) form of quetiapine, pimavanserin, and ziprasidone, averaging five to six hours [12-15].

The bioavailability of two drugs, lurasidone and ziprasidone, increases two- to threefold in the presence of food, hence their manufacturers' recommendations that they be taken with a meal [10,14]. In the case of ziprasidone, it is not possible to compensate for the food effect by doubling the dose because in the absence of food, the increase in plasma level is not proportional to the oral dose [16]. The XR formulation of quetiapine shows a 50 percent increase in absorption with a high-fat meal, which the manufacturer recommends avoiding [13]. Other drugs of this class may be dosed without regard for food. Use of drugs that require a meal or avoidance of a meal for optimal absorption may be most appropriate for patients who are cooperative and cognitively intact, and require sufficient patient education to ensure that patients and/or caregivers administer them correctly.

Metabolic activation and clearance — Most antipsychotic drugs are metabolized primarily via the cytochrome P450 system of the liver, although they differ as to which and how many enzymes are involved, giving them somewhat different susceptibility to liver impairment and drug-drug interactions. (See 'Drug-drug interactions' below.)

The notable exception to this rule is paliperidone, 80 percent of which is excreted unchanged via the kidneys, with only about 10 percent inactivated by hepatic enzymes [17]. As a result, paliperidone is the only medication of this class for which no dose adjustment is recommended in patients with impaired liver function [18,19]. The dose must be reduced, however, with mild to moderate renal dysfunction, and the drug is not recommended with severe renal impairment.

Clearance half-life affects how long it takes to achieve steady-state serum levels of a medication and the frequency of dosing required to maintain those levels. Shorter half-lives allow more rapid dose adjustments, but require more frequent drug administration. The most rapidly

metabolized drugs are quetiapine and ziprasidone, each with a clearance half-life of six to seven hours [11,14]. Ziprasidone is recommended exclusively for twice-daily dosing on this basis. Quetiapine's active metabolite N-desalkyl quetiapine, in contrast, has a 12-hour clearance half-life that gives the drug a longer period of clinical effectiveness and allows it to be dosed once daily. Aripiprazole, brexpiprazole, and cariprazine [20-22] have the longest clearance half-lives at 75 hours, 91 hours, and two to four days, respectively. The majority of cariprazine's clinical activity appears to be due to an active metabolite with a clearance half-life of one to three weeks. These longer clearance times give the drugs relatively stable levels with once-daily dosing, but extend the time required to make dose adjustments or to clear them completely during transitions off the medication.

The presence of active metabolites may extend the effective duration of clinical activity beyond that expected for the clearance half-life of the parent compound. The consequences in patients with impaired metabolic function, who may experience either an increase in activity because of impaired clearance of the drug or decreased activity because of impaired conversion to an active metabolite, are less predictable.

SGAs with active metabolites include aripiprazole, iloperidone, lurasidone, pimavanserin, and risperidone [10,11,15,20,22-24]. Risperidone's metabolite 9-hydroxyrisperidone, is marketed separately as paliperidone [17]. The overlap in activity of these two drugs appears to contribute to similar clinical responses and side effects seen with the two drugs.

Patients with genetic variants of CYP 2D6 may be either poor or extensive metabolizers of some drugs [25]. Significant differences in clearance half-lives and associated serum levels based on these genetic polymorphisms have been reported for aripiprazole, brexpiprazole, clozapine, and iloperidone [20,21,23,26]. In the case of clozapine, the resulting clearance half-lives range from 4 to 66 hours. For aripiprazole and iloperidone, the difference in clearance half-lives between poor and extensive metabolizers is about twofold. Despite these differences, CYP 2D6 phenotyping or genotyping have not yet demonstrated clinical utility, and the most effective approach to address these differences is to determine a serum drug level when poor or extensive metabolism is suspected [25]. In poor metabolizers, dose reductions of 50 percent have been recommended for aripiprazole, brexpiprazole, and iloperidone [20,21,23]; dose reduction is also recommended for poor metabolizers of clozapine [26].

Drug-drug interactions — Most SGAs depend on cytochrome P450 enzymes for metabolism, and some have significant increases or decreases in serum levels when used with inducers or inhibitors of these enzymes (table 2). As a general rule, however, these interactions are mild and readily manageable with dose adjustments as noted below. A list of common medications that are significant inhibitors or inducers of CYP 3A4 is provided in the table (table 3). In a

few cases, specific medications with overlapping side effects should be avoided, most notably those with cardiac, sedative, anticholinergic, or metabolic risk. Even in these cases, however, the risk is relative and can usually be managed without a radical change in treatment. The most noteworthy interactions are described below:

- **Aripiprazole** – Dopamine D2 receptor blockade may be unpredictable when the partial agonist aripiprazole is given simultaneously with other antipsychotics (all of which are dopamine antagonists), as might occur during a transition between medications. This can lead in some cases to a paradoxical reduction in dopamine blockade and reduced antipsychotic effect as the dose of aripiprazole is increased. Aripiprazole is metabolized via CYP 2D6 and CYP 3A4. The manufacturer recommends a twofold dose increase in the presence of metabolic inducers such as carbamazepine [10,20] and a 50 percent reduction in dose with inhibitors such as fluoxetine, quinidine, or ketoconazole.

- **Asenapine** – With substantial metabolism occurring through both CYP 1A2 and glucuronidation, drug interactions involving asenapine tend to be mild and generally do not require an adjustment in dose [9]. Mild interactions are possible with medications having similar side effects, such as sedation, weight gain, or Parkinsonism.

- **Brexpiprazole** – The drug is metabolized by CYP 2D6 and CYP 3A4; inhibitors of either enzyme cause a twofold increase in serum levels, and the CYP 3A4 inducer rifampin caused a 75 percent reduction in serum level [21]. The manufacturer recommends dose adjustments accordingly. As with aripiprazole, the combination of this dopamine partial agonist with a dopamine antagonist can lead to unpredictable levels of dopamine D2 receptor blockade and a paradoxical reduction in efficacy when the drug is combined with a dopamine antagonist. However, when compared with aripiprazole, brexpiprazole has lower intrinsic activity at the dopamine D2 receptor [27].

- **Cariprazine** – Both the parent drug and its active metabolites are primarily eliminated via CYP 3A4, and are susceptible to changes in the activity of that enzyme. A dose reduction of 50 percent is recommended in the presence of CYP 3A4 inhibitors [22]. The effect of CYP 3A4 inducers has not been evaluated.

- **Clozapine** – Drug-drug interactions are significant with clozapine and can arise through several possible mechanisms [26]. Metabolism occurs primarily via CYP 1A2 and CYP 3A4, with a smaller contribution from CYP 2D6; strong CYP 1A2 inhibitors, such as fluvoxamine or ciprofloxacin, may require a reduction to one-third of the original dose.

  Because of clozapine's risk of agranulocytosis and its strong anticholinergic, sedative, cardiac, and hypotensive properties, other agents with these characteristics should be

avoided or used with care. Smokers may require a twofold increase in dose compared with nonsmokers, and a reduction of 30 to 40 percent may be required when a smoker is admitted to a hospital or other nonsmoking environment.

- **Iloperidone** – Plasma levels of iloperidone increase with CYP 2D6 and CYP 3A4 inhibitors, and the manufacturer recommends that the dose be reduced by 50 percent in the presence of medications such as fluoxetine, paroxetine, or ketoconazole [23].

- **Lumateperone** – This drug is metabolized by primarily by CYP 3A4, along with 2C8 and 1A2 enzymes. Dose adjustments should be made for individuals treated with CYP 3A4 inhibitors. Avoid use with inducers of CYP 3A4.

- **Lurasidone** – The major route of metabolism of lurasidone is via CYP 3A4. Medications that are strong inhibitors or inducers of CYP 3A4 such as rifampin or ketoconazole substantially alter serum levels of lurasidone and their coadministration is contraindicated [10]. Dose reduction is recommended in the presence of moderate CYP 3A4 inhibitors, such as diltiazem.

- **Olanzapine** – Drug-drug interactions are not prominent with olanzapine, but the medication is dependent on CYP 1A2 for clearance [12]. Coadministration of medications that strongly inhibit or induce CYP 1A2 can alter olanzapine levels.

  Olanzapine levels are decreased somewhat by cigarette smoking, which may be an issue when a patient is in a nonsmoking environment such as a hospital or resumes smoking upon discharge.

- **Paliperidone** – This drug is not dependent on hepatic metabolism and therefore has no significant drug interactions based on enzyme induction or inhibition [17,24]. However, it may be necessary to increase the dose of paliperidone when a strong inducer of both CYP 3A4 and P-glycoprotein 1 (eg, carbamazepine, rifampin, St. John's wort) is co-administered. Conversely, on discontinuation of the strong inducer, it may be necessary to decrease the dose of paliperidone. Mild interactions are possible with medications having similar side effects, such as sedation, weight gain, or Parkinsonism.

- **Pimavanserin** – The major route of metabolism of this drug is via CYP 3A4 and to a lesser extent CYP 3A5, both of which convert it to an active metabolite. Dose adjustment is recommended when the drug is used simultaneously with strong 3A4 inhibitors [15]. Additionally, the drug is not recommended for use with other agents that may prolong QT interval.

- **Quetiapine** – Drug-drug interactions are not commonly reported with quetiapine, but serum levels are affected by induction or inhibition of CYP 3A4, and the manufacturer recommends up to a fivefold increase in dose with inducers such as carbamazepine and a reduction to one-sixth the dose with strong CYP3A4 inhibitors such as voriconazole or ritonavir [11,13]. A list of strong inhibitors and inducers of CYP3A4 is provided in a table (table 3). Side effects may worsen when the drug is combined with other agents that cause sedation, anticholinergic effects, hypotension, or weight gain.

- **Risperidone** – Drug-drug interactions involving risperidone are infrequent, but it is metabolized primarily through CYP 2D6, and its serum levels are increased by strong CYP2D6 inhibitors such as fluoxetine and paroxetine, and to a lesser degree by bupropion [24]. Although it is not routinely necessary to adjust the dose of risperidone whenever such a medication is added or withdrawn, clinicians should be aware of the potential for a change in serum level with the simultaneous use of these medications.

- **Ziprasidone** – Metabolic clearance of ziprasidone occurs mostly via glutathione and aldehyde oxidase, with a minor contribution from CYP 3A4, so inhibitors and inducers of the cytochrome P450 system show only modest effects [14]. QT prolongation may be an issue if used with other drugs having similar cardiac effects. (See 'QTc interval prolongation and sudden death' below.)

Interactions of SGAs with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact) included in UpToDate.

ADMINISTRATION

Several second-generation antipsychotic (SGA) medications are available in other formulations in addition to a standard oral tablet (table 2):

- **Orally disintegrating tablets** are available for aripiprazole, asenapine, clozapine, olanzapine, and risperidone. This formulation is especially useful for patients who have trouble swallowing pills or who are suspected of "cheeking" or concealing tablets in their mouths and disposing of them. These tablets dissolve rapidly in a minimal amount of saliva, making this form of non-adherence nearly impossible. With the exception of asenapine, none of these medications is absorbed transmucosally, and their bioavailability and rate of absorption are identical to those of standard tablets.

- **Immediate-release injectable** formulations of olanzapine, and ziprasidone are available for intramuscular administration. These medications are appropriate for emergency

situations, such as an agitated, acutely psychotic patient. None of the SGAs is available for intravenous use.

- **Long-acting, injectable antipsychotics** are used to treat patients unable to adhere to daily regimens. Long-acting versions of aripiprazole, olanzapine, paliperidone, and risperidone may be administered by injection at two-week to three-month intervals. Administration of long-acting antipsychotics is described in a table (table 4) and discussed further separately. (See "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

Oral dosing of SGAs with standard or orally disintegrating tablets is the preferred route of administration in most patients. These formulations have equivalent dosing, absorption, and clearance. A table describes the usual oral starting dose, dose range and maximum dose, dose adjustments, formulations, half-life, and more common hepatic enzyme effects of these medications (table 2).

Once-daily dosing is indicated for most of these medications (exceptions include asenapine, iloperidone, and ziprasidone). More frequent administration may be useful in some cases to minimize side effects. Dosing at bedtime is generally preferred because of the sedation associated with many of these drugs, but exceptions are common and the medications work equally well irrespective of the time of the dose. (See 'Sedation' below.)

ADVERSE EFFECTS

Common side effects associated with second-generation antipsychotics (SGAs) include weight gain and related metabolic effects, hypotension, sedation, anticholinergic symptoms, hyperprolactinemia, extrapyramidal symptoms (EPS), cardiac effects, cardiomyopathies, cataracts, and sexual dysfunction. The rate and severity of most of these side effects vary across SGAs and are described in a table (table 1) and in the paragraphs below. These differences in side effect profiles often influence the selection among antipsychotic drugs. As examples:

- A patient whose symptoms include insomnia may benefit from a sedating antipsychotic.
- A patient with diabetes should avoid medications with a high risk of weight gain and metabolic effects.
- A patient with a known cardiac problem or taking medications that prolong QT interval should preferentially receive an antipsychotic with a more favorable cardiac profile.

- A patient with essential hypertension may do well with an antipsychotic with hypotensive effects.

Rare but serious side effects include tardive dyskinesia, neuroleptic malignant syndrome, seizures, agranulocytosis, hypersensitivity reactions, and an increased risk of mortality from all causes, especially in older adult patients with dementia-related psychosis.

The management of antipsychotic drug side effects is discussed separately.

- (See "Neuroleptic malignant syndrome".)
- (See "Tardive dyskinesia: Prevention, treatment, and prognosis".)
- (See "Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy".)
- (See "Breastfeeding infants: Safety of exposure to antipsychotics, lithium, stimulants, and medications for substance use disorders".)
- (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)

Metabolic syndrome — Weight gain, diabetes, and dyslipidemia are the components of metabolic syndrome usually associated with SGAs, along with the consequent risks of diabetic ketoacidosis and cardiovascular disease [28-30]. The mechanism by which these symptoms are produced is not entirely clear, but there is evidence for both increased appetite and altered metabolic control with these drugs [31]. Patient-related factors include pre-existing metabolic issues, and those who are obese, diabetic or prediabetic, or have high-risk lipid profiles are more likely to experience problems with these medications than other patients. In addition, there is evidence of increased susceptibility in patients with some of the disorders they treat, particularly schizophrenia [32]. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Although no SGA is entirely free of these metabolic effects, there are major differences in their prevalence among the medications [33]. Clozapine and olanzapine [28-30] carry significantly higher risk than other antipsychotics, whereas aripiprazole [34], lurasidone [10], pimavanserin [15], and ziprasidone [35,36] are associated with the lowest risk (table 1). The potential morbidity of these symptoms has led to recommendations for routine short- and long-term monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profile of patients taking any of the antipsychotic drugs (table 5) [37].

Anticholinergic effects — Antimuscarinic activity occurs with several SGAs or their active metabolites and can result in anticholinergic symptoms with those drugs, mostly reported as

dry mouth or constipation and less often as blurred vision or urinary retention. In the case of clozapine, sialorrhea rather than dry mouth is common, possibly because of drug effects at dopamine D4 or alpha2A adrenergic receptors [38,39], but other anticholinergic effects follow the expected pattern.

Clozapine has the strongest affinity for muscarinic receptors among the SGAs, and patient reports of side effects are most frequent and severe with this drug [26]. Among the other SGAs, olanzapine [12] and quetiapine [11,13] have higher rates of anticholinergic problems than the remaining medications, among which these issues are uncommon.

For most patients, no special monitoring is required. For patients on clozapine, in contrast, regular inquiries regarding urinary retention, blurred vision, and especially constipation should be made. Aggressive treatment of constipation, often including prophylactic agents, may be required to avoid serious side effects, such as fecal impaction or bowel perforation [35,40]. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Adverse effects'.)

Cardiovascular events

QTc interval prolongation and sudden death — Several SGAs are known to cause prolongation of the QT interval, hypothesized to occur via direct inhibition of the cardiac delayed potassium rectifier channel, which extends the ventricular repolarization process [36]. QT prolongation increases the risk of torsade de pointes and potentially lethal arrhythmias. Sudden death, usually attributed to this process, has been reported in 1.5 to 1.8 persons per 1000 years of exposure to these drugs, more than twice the rate of age-matched controls [36,41]. A corrected QT interval (QTc) greater than 500 ms or an increase in QTc of 60 ms or more during antipsychotic treatment indicates significant risk for torsade de pointes [42,43]. (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

Specific SGAs and their association with QT interval prolongation include:

- Ziprasidone appears to have a somewhat greater risk of QT prolongation than other SGAs [14,44,45]. Cases of prolonged QT interval have been reported in conjunction with other risk factors, such as pre-existing QT prolongation, other cardiovascular disease, hypokalemia, or concurrent use with other drugs that prolong QT interval [36,46]. Low to moderate QT prolongation is also a side effect of pimavanserin and iloperidone [15,23].

  An electrocardiogram (ECG) is recommended in patients with known risk factors prior to initiation, when the drug reaches a steady state therapeutic level, and if any new cardiac symptoms occur.

Discontinuation of the medication is recommended for a QTc meeting the criteria listed above [46].

- Quetiapine has been associated with QT prolongation in cases of overdose and carries a cautionary statement regarding use in patients with cardiac risk [47], as do asenapine and paliperidone [17,20].

- Olanzapine and risperidone have each been associated with mild QT prolongation, but neither carries a specific caution on this issue [12,24].

- Lurasidone [10,48], aripiprazole [20], brexpiprazole [21], and cariprazine [22] are the least likely to cause cardiac arrhythmias, but one case of QT prolongation and cardiac death was reported with aripiprazole in a patient with no known prior risk factors [49].

Routine monitoring of ECG with antipsychotics is not usually required in patients without cardiac risk factors. In patients with cardiac risk factors, including individuals taking other medications known to prolong QT interval, no SGA is completely without risk and appropriate caution should be exercised.

Myocarditis and cardiomyopathy — Clozapine has been associated with potentially fatal cases of myocarditis and cardiomyopathy, most often in the first few weeks or months of treatment [50,51]. The annual incidence of myocarditis with clozapine has been reported over a wide range, with a mortality rate of 0.01 to 0.1 percent. The mechanism is not clear but may be due to a drug hypersensitivity reaction. Monitoring for myocarditis in patients taking clozapine is suggested and described separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Adverse effects' and "Schizophrenia in adults: Guidelines for prescribing clozapine".)

Rare cases of myocarditis and cardiomyopathy have been reported with quetiapine, risperidone, and ziprasidone.

Orthostatic hypotension — Alpha-adrenergic blockade is the likely mechanism of orthostatic hypotension with SGAs. The condition is often accompanied by orthostatic tachycardia, both of which are most common in the first few days of exposure to the medications or when the dose is being increased.

Changes in blood pressure and heart rate are observed most frequently with clozapine [26], iloperidone [23], quetiapine [11,13], and paliperidone [17], and somewhat less often with olanzapine [12], risperidone [24], and ziprasidone [14]. They occur only rarely with aripiprazole [20], asenapine [9], brexpiprazole [21], cariprazine [22], lurasidone [10], and pimavanserin [15].

The symptoms are generally benign and self-limiting, but in some cases they may necessitate a slowing in the rate of dose titration, division of a single daily dose into two or three smaller doses, or a change in medication. Blood pressure and heart rate should be monitored during initiation of treatment, at three months, and annually thereafter. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Orthostatic changes and tachycardia'.)

Extrapyramidal symptoms — The defining difference between SGAs and their predecessor first-generation antipsychotics (FGAs) is a reduced incidence of the akathisia, rigidity, bradykinesia, dysphagia, tremor, and acute dystonic reactions that constitute extrapyramidal symptoms (EPS). As dopamine D2 antagonists or partial agonists, these drugs have the potential to interfere with dopamine transmission via the nigrostriatal tract, which is involved in control of muscle movement, thereby producing symptoms similar to those seen in Parkinson's disease. (See 'Pharmacology' above.)

Among the SGAs, risperidone carries the highest risk of EPS (8 to 25 percent in adults), especially at doses greater than 4 mg/day [24,52,53]. In postmarketing, cases of extrapyramidal symptoms have been reported in individuals concomitantly taking methylphenidate and risperidone when there was a change (either an increase or decrease) in dosing of either or both medications [54]. Elevated risk is also noted with aripiprazole [20], asenapine [9], cariprazine [22], lurasidone [10], and paliperidone [17]. Quetiapine, iloperidone, pimavanserin, and clozapine are the preferred agents in patients at high risk for EPS, including those with pre-existing movement disorders from other causes [55].

Patients on SGAs should be asked about restlessness, slow movements, shaking, and rigidity at baseline and weekly during dose increases. The Barnes Akathisia Scale or Simpson Angus Scale may be useful in documenting akathisia and parkinsonism. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Extrapyramidal symptoms'.)

Tardive dyskinesia — Tardive dyskinesia (TD) is reviewed here briefly and discussed in detail separately. (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis" and "Tardive dyskinesia: Prevention, treatment, and prognosis" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Tardive dyskinesia'.)

TD is characterized by involuntary choreoathetoid movements of the mouth, tongue, face, extremities, or trunk, including lip-smacking, tongue writhing or thrusting, jaw movements, facial grimacing, and trunk or extremity writhing. TD risk increases with age, time of exposure to the medications, and prior development of EPS. Although the symptoms are often mild and

of limited concern to the patient, they are sometimes progressive and may become disfiguring or disabling.

SGAs are significantly less likely to cause TD than FGAs [56]. Although there are limited data on the relative risk of TD among the different SGAs, there is evidence that TD risk may be similar to the prevalence of EPS, thus risperidone, paliperidone, aripiprazole, asenapine, and lurasidone may carry somewhat higher risk and quetiapine and iloperidone somewhat lower risk. In contrast to other SGAs, clozapine has not been shown to cause TD.

Patients on these medications should be formally assessed for TD at least annually; high-risk patients, such as those with prominent EPS or older adults, should be assessed every six months. Standardized assessments, such as the Abnormal Involuntary Movement Scale, are especially helpful in tracking development and progression of symptoms.

Seizure — Seizures have been reported with several SGAs, and consequently all of the drugs carry a standard warning about seizure risk. There is little evidence that they cause new-onset seizures, but rather they appear to lower seizure threshold in individuals already at risk. Clozapine has a dose-dependent 3 percent overall annual incidence of seizure, the highest among the SGAs [26,57]. Risperidone may also have a somewhat higher incidence than other SGAs [24], but direct comparative data are lacking. Seizures are rare with the other drugs. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Seizures'.)

Clozapine should be used with caution and in consultation with a neurologist in patients with known seizure disorders. In other patients, a review of the risks prior to treatment, attention to the patient's compliance with antiepileptic treatment, and consideration of antiepileptic dose adjustment are indicated. (See "Overview of the management of epilepsy in adults", section on 'Maximizing the likelihood of a successful outcome'.)

Cataracts — Concern about cataracts in patients taking antipsychotics is based on a known risk associated with the FGA chlorpromazine and from cataract development in beagles, but not other species, during the preclinical testing of quetiapine [46]. Subsequent population-based studies have detected no increased risk with quetiapine or other SGAs, and one study found evidence that SGAs reduce the likelihood of cataract surgery [58]. (See "Cataract in adults".)

Rare instances have been reported of cataracts in patients taking iloperidone [23], quetiapine [11,13], and ziprasidone [14]. Somewhat related cases of intraoperative floppy iris syndrome have been reported during cataract surgery with paliperidone and risperidone [17,24].

Despite the tenuous evidence of risk, the manufacturer recommends that patients taking quetiapine undergo a slit-lamp examination shortly after initiation of treatment and every six

months thereafter [11,13]. More generally, ocular examinations are recommended every two years in younger patients on SGAs and annually in patients over 40.

Prolactin elevation — Prolactin secretion in men and women is largely controlled via the inhibitory effect of tuberoinfundibular dopamine on the pituitary. Direct blockade of pituitary dopamine receptors allows uninhibited secretion of prolactin. Clinical consequences of elevated prolactin levels include gynecomastia, galactorrhea, menstrual disturbances, sexual dysfunction, and infertility, partially mediated through reduced estrogen and testosterone levels [59]. (See "Causes of hyperprolactinemia".)

Among the SGAs, risperidone [24] and paliperidone [17] are most strongly associated with elevated prolactin, and to a lesser degree asenapine [9], olanzapine [12], and ziprasidone [14]. Aripiprazole, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, pimavanserin [15], and quetiapine show little or no change in prolactin levels. Risperidone has also been associated with a significantly increased risk of pituitary adenoma (0.5 per 1000 patients) compared with other antipsychotics [60].

Patients on risperidone and paliperidone should be asked about changes in sexual function and abnormal lactation at each visit for 12 week and annually thereafter. A serum prolactin level is indicated if the patient develops signs of sexual dysfunction or galactorrhea [24,46]. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Endocrinologic and metabolic side effects'.)

Neuroleptic malignant syndrome — The pathognomonic features of neuroleptic malignant syndrome (NMS) are fever, muscle rigidity, mental status changes, and autonomic instability, generally accompanied by rhabdomyolysis and creatine kinase elevation [61,62]. The condition is rare but potentially fatal and constitutes a medical emergency. The physiological mechanism of NMS is unknown. (See "Neuroleptic malignant syndrome".)

No differences have been demonstrated in risk of NMS among the SGAs, all but the newest of which have case reports of the syndrome. The single strongest predictive factor is a prior episode of NMS. Other frequently cited factors include recently initiated treatment, aggressive dosing, parenteral administration, acute medical illness, and dehydration.

The most important element of prevention is to screen patients for prior episodes of NMS. The syndrome should be suspected if more than one of the essential features is present, and further evaluation should take place in a medical emergency department.

Sexual side effects — Dysfunction in all phases of sexual activity (libido, arousal, and orgasm) is common with antipsychotic treatment. Several pharmacologic mechanisms are likely to

contribute to sexual problems, including loss of desire through inhibition of dopaminergic motivation and reward pathways, erectile dysfunction through alpha-adrenergic blockade and anticholinergic activity, and impairment in desire, arousal, and orgasm due to prolactin elevation [63].

A 2011 meta-analysis of studies of patients taking SGAs found that 40 to 60 percent of patients taking clozapine, olanzapine, or risperidone reported sexual side effects, and those on aripiprazole, quetiapine, and ziprasidone experienced lower but still significant rates of 16 to 27 percent [64]. Further stratification was suggested by a more recent study [63], which found:

- 60 to 70 percent of patients taking paliperidone and risperidone experienced sexual side effects
- 50 to 60 percent of those on olanzapine, quetiapine, and ziprasidone
- Less than 50 percent on clozapine
- 16 to 27 percent on aripiprazole

Lower rates of sexual problems were found in clinical trials submitted to the US Food and Drug Administration (FDA) for regulatory approval of individual drugs (ranging from 0 to less than 4 percent) [12,14,20,24]. This may be due to patient reluctance to report sexual side effects spontaneously in the trials and the occurrence of an overall reduction in sexual function among individuals with schizophrenia, independent of treatment [65].

Clinicians should specifically ask about difficulties with sexual functioning initially and at least annually thereafter [46]. The 2011 meta-analysis above found that among patients who experienced sexual dysfunction secondary to an antipsychotic drug, switching to aripiprazole was more often associated with resolution of sexual dysfunction compared with when patients switched to another antipsychotic [63]. Other options for addressing these problems include evaluation for prolactin elevation, and standard treatments for sexual dysfunction caused by other medications. (See "Causes of hyperprolactinemia" and "Treatment of male sexual dysfunction" and "Overview of sexual dysfunction in females: Management" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Other treatment-emergent side effects and their treatment'.)

Sedation — All SGAs except pimavanserin are histaminic H1 receptor antagonists and thus have potential to cause drowsiness. As with other antihistamine-induced somnolence, the effect is most severe early in treatment, and tolerance usually develops within a few days [66]. Some SGAs (eg, lurasidone) have lower affinity to H1 and are associated with sedation/somnolence related to alpha adrenergic antagonism.

Sedation is most prominent with clozapine [26,67] and quetiapine [68-70], occurring in up to half of patients. Asenapine [9], lurasidone [10], olanzapine [12], and ziprasidone [14] have intermediate rates, typically reported in the 10 to 25 percent range. Other medications, including aripiprazole, brexpiprazole, cariprazine, paliperidone, pimavanserin, and risperidone, cause sedation in fewer than 10 percent of patients. Aripiprazole is unique in that 18 percent of patients report insomnia, about three times the number that report drowsiness [20].

Patients should be warned about drowsiness with the first few doses of treatment and should be asked about the side effect during the initial follow-up visit. Patients who experienced sedation early in treatment should be asked about it periodically thereafter. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Sedation' and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Orthostatic changes and tachycardia'.)

Falls — Antipsychotic medications may cause falls and fractures as the result of somnolence, postural hypotension, and/or motor and sensory instability cause falls and fractures as the result of somnolence, postural hypotension, and/or motor and sensory instability [71,72]. As an example, in a sample of 70,718 persons in Finland diagnosed with Alzheimer's disease between 2005 and 2011, new users of antipsychotic medication had an increased risk of hip fractures (adjusted hazard ratio = 1.54; 95% CI 1.39-1.70) from the first days of use [73].

For patients with conditions or taking medications that could exacerbate these effects [74], the FDA recommended that a fall risk assessment be completed when initiating antipsychotic treatment and recurrently for patients continuing on long-term antipsychotics.

Increased risk of mortality — There is consistent evidence for increased risk of death from any cause with the use of antipsychotics in all populations. Since 2005 the FDA has required that each SGA carry a "black box" warning of a 1.6- to 1.7-fold increase in mortality from all causes for older adult patients with dementia-related psychosis [75]. The warning was based on the FDA's review of 17 placebo-controlled trials of olanzapine, aripiprazole, risperidone, or quetiapine to treat dementia-related behavioral problems. Subsequent population-based studies confirmed these findings for this group [76,77]. Among these patients, specific causes of death included cardiac disorders (25 percent), cerebrovascular disease (8 percent), pulmonary disease (8 percent), cancer (7 percent), and diabetes (3 percent) [76].

Subsequent studies have found evidence that increased mortality risk involves a wide range of causes of death and occurs across all ages. As examples:

- A study of 183,392 antipsychotic users with a similar number of psychiatric patients not using antipsychotics and 544,726 general population controls found that the risk is not

related to dementia or to older age, but that younger patients with any diagnosis have a 4.1-times greater risk of mortality than age-matched peers, compared with a 1.4- to 1.8-fold increase for patients 65 years and older [78]. Causes of death were similar to those in older patients, with cardiovascular disorders accounting for 39 percent, respiratory 13 percent, neurological 9 percent, accidents 4 percent, gastrointestinal 3 percent, and genitourinary 3 percent.

- A study looking specifically at acute kidney injury in older adult patients on antipsychotics found a similar increased risk, suggesting that other organ systems are also vulnerable [79].

- A 2018 study of 189,361 children and youths ages 5 to 25 years enrolled in Medicaid between 1999 and 2014 who received antipsychotic doses greater than the equivalent of 50 mg per day of chlorpromazine (approximately 1.5 mg per day of olanzapine or 0.5 mg per day of risperidone [80]) were found to have 3.5-fold greater risk of death from medical causes. The mortality rate of those receiving antipsychotics at lower doses did not differ from age-matched controls, nor was the excess mortality attributable to accidents or suicides, which were comparable in all groups [81].

Studies comparing the relative risk of various antipsychotics have consistently shown that SGAs cause somewhat lower mortality than the FGAs (relative risk 0.5 to 0.8) [77,78,82]. Among the SGAs, one large population-based cohort study limited to older adult dementia patients found no differences among aripiprazole, olanzapine, risperidone, and ziprasidone, but a 20 percent lower risk with quetiapine [82]. These findings have not yet been replicated.

No specific monitoring has been suggested to address mortality risk in general, but the preponderance of vascular disorders suggests that attention to cardiac and metabolic issues may be helpful (table 5). In addition, it is critical that patients receiving antipsychotic medications have access to high-quality primary care services for health maintenance. (See 'Metabolic syndrome' above and 'Cardiovascular events' above.)

The association of SGAs with sudden cardiac death is described above. (See 'QTc interval prolongation and sudden death' above.)

Agranulocytosis — Neutropenia, leukopenia, and agranulocytosis with clozapine are well documented. This potentially fatal condition is most common in the first few months of treatment, in patients with pre-existing low cell counts, and in those who have previously experienced drug-induced blood dyscrasias. About 3 percent of clozapine-treated patients will show evidence of leukocytosis, and nearly 1 percent will develop agranulocytosis [83]. In the United States and other countries, regulations require routine monitoring of clozapine patients

for neutropenia and discontinuation of the drug in severe cases. Neutropenia and monitoring with clozapine are discussed in detail separately. (See "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Neutropenia/agranulocytosis' and "Schizophrenia in adults: Guidelines for prescribing clozapine", section on 'Neutrophil count'.)

Lower rates of these disorders are found with other antipsychotics. Reports of leukocytosis and neutropenia occur in up to 4 percent of patients receiving risperidone [24], 2 percent of those on paliperidone or quetiapine [11,17], and less than 1 percent of patients taking other SGAs. Cases of severe neutropenia or agranulocytosis have been reported but are rare.

For patients taking other SGAs who either have previously experienced a drug-induced leukocytopenia or have a pre-existing low WBC count or low ANC, monitoring is recommended during the first few months of treatment. Although no specific frequency for monitoring has been recommended, a reasonable approach would be an ANC at baseline, after one to two weeks, and after three to six months.

Hypersensitivity syndrome — Although allergic reactions have been reported with most SGAs, a specific warning has been issued regarding a potentially fatal drug reaction with eosinophilia and systemic symptoms (DRESS) for ziprasidone [84-87] and olanzapine [88]. More recently, Health Canada reviewed 11 case reports of DRESS with other second-generation antipsychotics and concluded that "there may be a link between the risk of DRESS and the use of clozapine, quetiapine, risperidone, aripiprazole, paliperidone and lurasidone" [89]. A safety alert has likewise been issued regarding serious allergic reactions with asenapine [90]. (See "Drug reaction with eosinophilia and systemic symptoms (DRESS)".)

Hypothyroidism — A 2018 Norwegian study of 345 patients and 989 healthy controls found that the use of either olanzapine or quetiapine, but not aripiprazole or risperidone, was associated with lower levels of free T4, but no change in thyroid-stimulating hormone levels. No clinical symptoms of hypothyroidism other than weight gain, a known side effect of olanzapine and quetiapine, was found. Of note, patients in the sample using antidepressant medications showed a similar difference in free T4, as did patients taking multiple psychotropic medications [91]. The clinical significance of this finding remains to be demonstrated.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Psychotic disorders".)

SUMMARY AND RECOMMENDATIONS

- **Selection** – With the exception of clozapine, second-generation antipsychotics (SGAs) have comparable efficacy for psychosis. SGAs differ from one another in pharmacokinetics, side effect profiles, formulations, and costs, all of which can be important considerations in selecting the best antipsychotic drug for a patient (table 1). (See 'Introduction' above.)

- **Pharmacology** – The mechanism of action of most SGAs appears to be postsynaptic blockade of brain dopamine D2 receptors. Most SGAs differ from older antipsychotic medications such as first-generation antipsychotics (FGAs) in that serotonin 5HT2 receptor binding exceeds their affinity for dopamine D2 receptors. Most SGAs depend on cytochrome P450 enzymes for metabolism, and some have significant increases or decreases in serum levels when used with inducers or inhibitors of these enzymes. (See 'Pharmacology' above.)

- **Adverse effects** – Select adverse effects include:

  - **Metabolic syndrome** – Weight gain and metabolic effects are the most prominent side effects of SGAs. Clozapine and olanzapine are strongly associated with these effects, whereas aripiprazole, lurasidone, and ziprasidone are the preferred agents to minimize these issues. All antipsychotics carry recommendations for routine monitoring of metabolic parameters (table 5). (See 'Metabolic syndrome' above and "Schizophrenia in adults: Maintenance therapy and side effect management".)

  - **Increased risk of mortality** – Increased mortality has been found with all SGAs across all ages and diagnoses. Patients who are at highest risk are those who are older or have longer times of exposure to the drugs. No differences in risk have been demonstrated within this class of medications. (See 'Increased risk of mortality' above.)

  - **Extrapyramidal symptoms and tardive dyskinesia** – SGAs have lower risks of extrapyramidal symptoms (EPS) and tardive dyskinesia than most FGAs. Risperidone is associated with a higher risk of EPS compared with other SGAs; clozapine, iloperidone, and quetiapine carry the lowest risk. (See 'Extrapyramidal symptoms' above.)

  - **Anticholinergic effects** – Anticholinergic effects of SGAs are most prominent with olanzapine, quetiapine, and clozapine. The most common side effects are dry mouth or constipation and, less often, blurred vision or urinary retention. (See 'Anticholinergic effects' above.)

- **Cardiovascular events** – Prolongation of the QT interval tends to be mild with SGAs but somewhat greater with iloperidone and ziprasidone than with other agents. We avoid these two medications in high-risk patients or those taking other QT-prolonging drugs. (See 'QTc interval prolongation and sudden death' above.)

- **Orthostatic hypotension** – Orthostatic hypotension is often accompanied by orthostatic tachycardia and is most common in the first few days of SGA administration or when the dose is increased. These are most commonly seen with clozapine, iloperidone, quetiapine, and paliperidone, less often with olanzapine, risperidone, and ziprasidone, and only rarely with aripiprazole, asenapine, brexpiprazole, and lurasidone. (See 'Orthostatic hypotension' above.)

- **Falls** – Treatment with SGAs can cause falls and fractures as the result of somnolence, postural hypotension, and/or motor and sensory instability. We monitor all individuals closely and complete a fall risk assessment at regular intervals. (See 'Falls' above.)

- **Sedation** – Sedation may occur with any SGA but is usually associated with clozapine, olanzapine, and quetiapine. Asenapine, lurasidone, and ziprasidone have intermediate rates while aripiprazole more often causes insomnia than sedation. (See 'Sedation' above.)

- **Prolactin elevation** – Primarily associated with risperidone and paliperidone, this occurs infrequently with olanzapine and ziprasidone, and is rare with other SGAs. A serum prolactin level is indicated if the patient develops signs of sexual dysfunction or galactorrhea. (See 'Prolactin elevation' above.)

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