First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects

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INTRODUCTION

Antipsychotic medications have been used since the 1950s to treat psychosis; they can be used to treat acute psychosis from any cause and to manage chronic psychotic disorders such as schizophrenia. As a class, antipsychotics are also effective in the treatment of acute agitation, bipolar mania, and other psychiatric conditions.

First-generation antipsychotics (FGAs), also known as neuroleptics, conventional or typical antipsychotics, have significant potential to cause extrapyramidal symptoms and tardive dyskinesia. This propensity to cause movement disorders is the primary difference between FGAs and second-generation antipsychotics (SGAs). In other respects, such as other side effects and their mechanism of action, the two classes have substantial overlap and comparable efficacy.

The pharmacology, administration, and side effects of FGAs are discussed here. The pharmacology, administration, and side effects of SGAs are discussed separately. The efficacy and administration of antipsychotic drugs for specific psychotic disorders are also described separately, as are antipsychotic poisoning, tardive dyskinesia, neuroleptic malignant syndrome, and other antipsychotic drug side effects.

- (See "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)
- (See "Schizophrenia in adults: Maintenance therapy and side effect management".)
- (See "Bipolar mania and hypomania in adults: Choosing pharmacotherapy".)
- (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)
- (See "Delusional disorder".)
- (See "Brief psychotic disorder".)
- (See "Treatment of postpartum psychosis".)
- (See "First-generation (typical) antipsychotic medication poisoning".)
- (See "Second-generation (atypical) antipsychotic medication poisoning".)
- (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis".)
- (See "Neuroleptic malignant syndrome".)

PHARMACOLOGY

The mechanism of action of all first-generation antipsychotics (FGAs) appears to be postsynaptic blockade of brain dopamine D2 receptors. Evidence supporting this mechanism includes strong antagonism of D2 receptors in both cortical and striatal areas [1], a high correlation between D2 receptor binding and clinical potency [2], and a consistent requirement of 65 percent D2 receptor occupancy for antipsychotic efficacy in functional imaging studies [3]. The nonspecific localization of FGA dopamine binding throughout the central nervous system is consistent with their risk of movement disorders and prolactinemia. Aside from their common activity as D2 antagonists, each FGA has distinct effects on neuronal 5-HT2a, alpha-1, histaminic, and muscarinic receptors, which generally correspond to their individual side effect profiles, as shown in the table (table 1).

High- and low-potency FGAs — The pharmacologic differences described above are the basis for the classification of FGAs as either high- or low-potency drugs:

- The high-potency FGAs (fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, and trifluoperazine) are dosed in the range of 1 to 10s of milligrams and have low activity at histaminic and muscarinic receptors. They are associated with little sedation, weight gain, or anticholinergic activity, but a high risk for extrapyramidal symptoms (EPS).

- The low-potency FGAs (chlorpromazine and thioridazine) are dosed in 100s of milligrams and have high histaminic and muscarinic activity with a corresponding increased prevalence of sedation and anticholinergic effects, but lower risk of EPS. Chlorpromazine

and thioridazine have significantly greater adverse effects (eg, blurred vision, ocular toxicity, orthostatic hypotension, QTc prolongation, and urinary retention) relative to other antipsychotics; generally, many better tolerated options are preferred to these low-potency FGAs. (See 'Side effects' below.)

Absorption and bioavailability — Oral absorption of the FGAs may be erratic and several of the drugs undergo extensive first-pass metabolism by the liver, yielding low or variable oral bioavailability. FGAs are lipophilic, highly protein- and tissue-bound as a class with large volumes of distribution. Each of these factors varies substantially among patients, making it difficult to predict serum drug levels based on dose alone. Meaningful guidelines for therapeutic drug levels have been similarly elusive, even for haloperidol, the most widely studied of these drugs [4,5]. Each of these factors should be considered as the clinician assesses the patient's clinical response to an initial dose of the medication.

The most readily absorbed FGAs are loxapine and perphenazine, with times to peak serum concentration of one to three hours. Other drugs are less predictably absorbed. An oral dose of haloperidol, for example, may require anywhere from two to six hours to reach peak concentration. The intramuscular formulation of loxapine requires five hours to be fully absorbed, more than twice as long as its oral counterpart. Loxapine has the highest bioavailability among these drugs at nearly 100 percent, in contrast to haloperidol at 60 percent and chlorpromazine's 20 percent. Predictable changes in bioavailability with food have not been reported with any of the drugs.

Loxapine has a unique aerosol formulation that reaches peak plasma concentration within two minutes following use, with little variation among subjects [6]. The clinical effect of the drug on psychotic agitation in schizophrenia and bipolar mania patients was reported within 10 minutes of administration [7,8]. (See 'Administration' below.)

METABOLIC ACTIVATION AND CLEARANCE

All FGAs are subject to extensive metabolism via the cytochrome P450 system, and several use an additional glucuronidation pathway. This dependence on hepatic clearance makes the drugs susceptible to liver impairment and drug-drug interactions. (See 'Drug-drug interactions' below.)

The CYP-2D6 gene is polymorphic and increased serum concentrations of perphenazine and haloperidol, as well as more prominent side effects, such as over-sedation, have been described among CYP-2D6 slow metabolizers [9,10]. In the case of pimozide, the maximum daily dose

should be reduced from 10 mg to 4 mg in slow metabolizers. No specific dose adjustments in slow or extensive metabolizers are recommended for other FGAs. Specific metabolic pathways used by individual drugs are listed in the table (table 2).

Most FGAs have clearance half-times of 20 to 40 hours, and several have active metabolites, factors that lead to relatively stable serum levels with once daily administration. Recommendations for more frequent dosing are usually based on side effect management rather than pharmacokinetics. The presence of active metabolites may complicate predictions of how long it will take a drug to be cleared, as in the case of loxapine, which has two active metabolites that give it more complex pharmacokinetics than other antipsychotics [11]. This is favorable in the case of perphenazine's active metabolite, 7-hydroxyperphenazine, whose 19-hour clearance time gives the medication a longer duration of activity than the relative short clearance half-time of the parent compound would suggest. A possible negative effect has been suggested for haloperidol's metabolite pyridinium, which has been cited as potentially neurotoxic [12]. Pharmacokinetics of the FGAs are described in the table (table 2).

Drug-drug interactions — The FGAs can interact with drugs that have potent effects on CYP metabolism, including the antidepressants fluoxetine, paroxetine, and bupropion, which inhibit CYP-2D6, and the mood stabilizer carbamazepine, which induces CYP-1A2 and -3A4 (table 2). The impact of CYP induction or inhibition on serum levels of most FGAs is moderated somewhat in the drugs that have multiple pathways for clearance, including chlorpromazine, haloperidol, loxapine, perphenazine, and thioridazine.

Fluphenazine has a single primary pathway via CYP-2D6 and is more susceptible to interactions with inhibitors of this enzyme than are other FGAs. Fluphenazine is not recommended for concurrent use with strong CYP-2D6 inhibitors. Pimozide levels are moderately sensitive to inhibition of CYP-2D6, but due to the risk for QTc-interval prolongation, the use of pimozide with strong CYP2D6 inhibitors is contraindicated.

Chlorpromazine is also sensitive to induction of CYP-1A2, such as occurs with heavy smoking, a quality it shares with thiothixene. A patient who is stabilized on one of these drugs in a nonsmoking environment, such as a hospital, may experience a drop in serum levels upon returning home and resuming smoking. In each of these cases, a moderate dose increase may be required [13-15].

ADMINISTRATION

Due to the propensity of first-generation antipsychotics (FGAs) to cause extrapyramidal symptoms and tardive dyskinesia, second-generation antipsychotics are typically the preferred choice over FGAs in the treatment of psychosis. This is discussed in detail elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management" and "Psychosis in adults: Initial management", section on 'Selection'.)

When used, oral dosing of FGAs is the preferred route of administration in most patients. A table describes the usual oral starting dose, dose range and maximum dose, and formulations (table 2). Once-daily dosing is indicated for most of the FGAs. 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 the drugs, but exceptions for individual patients are common and the medications work equally well irrespective of the time of the dose.

Loxapine is available for administration as a heat-generated aerosol of particles appropriate for deep lung delivery [6]. The drug is given as a single inhaled dose that is absorbed rapidly and completely. This formulation is approved for once-daily dosing for control of psychotic agitation. (See 'Absorption and bioavailability' above.)

Intramuscular injectable formulations of antipsychotic drugs for acute indications (table 3) and long-acting injectable formulations (table 4) are discussed separately. (See "Assessment and emergency management of the acutely agitated or violent adult" and "Schizophrenia in adults: Pharmacotherapy with long-acting injectable antipsychotic medication".)

SIDE EFFECTS

While all antipsychotic medications are believed to be comparable in effectiveness (with the exception of clozapine for treatment-resistant schizophrenia), they differ in side effect profiles, both individually and between first-generation (FGA) and second-generation (SGA) antipsychotics. The choice of an antipsychotic is often influenced by its side effect profile and its match with the patient's clinical status and vulnerabilities. As examples:

- A sedating antipsychotic, such as chlorpromazine, might be used for a patient with psychosis and insomnia.
- An antipsychotic associated with a lower risk of metabolic syndrome, such as haloperidol, might be selected in a patient with diabetes, hyperlipidemia, or obesity.

Common side effects associated with FGAs include extrapyramidal symptoms (EPS), tardive dyskinesia, hyperprolactinemia, neuroleptic malignant syndrome, QT prolongation, sudden

death, and an increased risk of mortality when used to treat psychiatric symptoms associated with dementia in older adult patients. A table shows the relative likelihood of many of these side effects for individual FGAs (table 1). Management of these side effects is described separately. (See "Tardive dyskinesia: Etiology, risk factors, clinical features, and diagnosis" and "Causes of hyperprolactinemia" and "Neuroleptic malignant syndrome" and "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management" and "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Side effect management'.)

Extrapyramidal symptoms — The defining difference between FGAs and the newer SGAs is their higher incidence of the akathisia, rigidity, bradykinesia, tremor, and acute dystonic reactions that constitute EPS. As dopamine D2 antagonists, 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 FGAs, the high-potency drugs fluphenazine, haloperidol, loxapine, pimozide, and thiothixene are usually associated with the highest risk of EPS. A systematic review found that 21 to 31 percent of patients treated with haloperidol for three to eight weeks experienced drug-induced EPS [16]. The low-potency medications chlorpromazine and thioridazine are less likely to cause EPS than are the high-potency drugs and in some studies show risk comparable to moderate or high doses of the SGA risperidone [17]. A review of schizophrenia treatments in the community found perphenazine to be associated with a lower rate of EPS than the high-potency FGA haloperidol and comparable to risperidone [18] (table 1).

Patients on FGAs 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 (table 5) can 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; the etiology, epidemiology, assessment, treatment, and prevention of tardive dyskinesia are 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.

TD has been reported with all FGAs at a cumulative rate of 5 percent per year, with higher risk in the older population [19-21]. The FGAs are considerably more likely to cause TD at all ages than are SGAs, a major reason that the newer drugs have largely supplanted them for maintenance use [22]. It is not clear if there are differences in risk among the FGAs, although the low-potency drugs chlorpromazine and thioridazine are generally thought to carry less risk based on their lower incidence of EPS. Higher risk has been attributed to fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine (table 1).

Patients on these medications should be formally assessed for TD every three to six months throughout their course of treatment; high-risk patients, such as those with prominent EPS or older adults, should be assessed at the shorter interval. Standardized assessments, such as the Abnormal Involuntary Movement Scale (AIMS) (form 1) are especially helpful in tracking development and progression of symptoms.

Metabolic syndrome — Weight gain, diabetes, dyslipidemia, diabetic ketoacidosis, and cardiovascular disease constitute a metabolic syndrome usually associated with SGAs, but presenting with comparable frequency in FGAs [23]. 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 [24]. Patient-related factors include preexisting 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. There is evidence of increased susceptibility in patients with some of the disorders they treat, particularly schizophrenia [25]. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Metabolic dysregulation'.)

Although no FGA is entirely free of weight gain and related metabolic effects, chlorpromazine appears to carry relatively high risk [26-29], whereas fluphenazine, haloperidol, and pimozide show the lowest risk (table 1) [12,30-32], followed by loxapine [33]. The potential morbidity of these symptoms has led to recommendations for routine monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profile of patients taking any of the antipsychotic drugs (table 6) [34].

Anticholinergic effects — Antimuscarinic activity is prominent with the low-potency FGAs chlorpromazine and thioridazine, and commonly results in dry mouth or constipation and less often in blurred vision or urinary retention. These symptoms tend to be mild or absent with the

higher-potency drugs. Although no specific monitoring is recommended, patient complaints should be addressed with dose adjustment, medication change, or appropriate medical intervention.

Cardiovascular events

QT interval prolongation and sudden death — Sudden death, believed in most cases to be caused by QT prolongation, has been reported in 1.5 to 1.8 persons per 1000 years of exposure to any antipsychotic drug, more than twice the rate of age-matched controls [35]. Among the first-generation antipsychotics (FGAs), chlorpromazine, thioridazine, and intravenous haloperidol are known to be more likely to prolong the QT interval, with pimozide posing an intermediate level of risk. The amount of prolongation is greatest with thioridazine and pimozide. Several reports, including a 2015 meta-analysis of observational studies found that thioridazine had the highest relative risk among both FGAs and second-generation antipsychotics (SGAs) at more than fourfold the rate of case controls [36-39]. Mesoridazine, an FGA with comparable risk for QT prolongation (and an active metabolite of thioridazine) [40], was discontinued by the manufacturer in 2004 because of this side effect and is no longer available.

The US Food and Drug Administration (FDA) and expert guidelines have recommended that thioridazine should not be used as a first-line treatment for psychosis. Prior to prescribing thioridazine, pimozide, or intravenous haloperidol, patients should receive an electrocardiogram (ECG) and serum potassium level. An ECG should be checked at least annually in patients taking the drugs, including during dose adjustments and in response to any changes in the patient's cardiac condition. These medications should not be started in a patient with a baseline corrected QT interval (QTc) greater than 450 ms. During treatment, a QTc greater than 500 ms or an increase in QTc of 60 ms or more indicates significant risk for torsade de pointe and merits a change in treatment, such as a dose reduction or switch to a lower-risk antipsychotic [41,42]. Inhibitors of CYP-2D6, such as fluoxetine and bupropion, should be avoided with thioridazine, as should drugs that prolong QT interval. (See "Acquired long QT syndrome: Clinical manifestations, diagnosis, and management".)

Although oral and intramuscular dosing of haloperidol have been associated with minimal change in QT interval, intravenous (IV) haloperidol has an elevated risk of prolonged QTc interval and torsades de pointes, especially at doses above 35 mg/day [43-45]. In addition to the initial tests and cautions described above, continuous cardiac monitoring is recommended during acute IV drug administration and for two to three hours thereafter [44-46]. Similar caution should be exercised with IV droperidol in patients who are medically ill, older adults, or

receiving other agents that prolong QT interval [44,47]. (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects".)

Pimozide prolongs the QT interval less severely [48], but has been associated with cardiac death in the presence of metabolic inhibitors of CYP-3A4, specifically clarithromycin, and in theory, other macrolide antibiotics, antifungals such as ketoconazole, and verapamil [49]. For this reason, similar cautions are recommended [50].

Loxapine and thiothixene show only slight changes in QT interval at standard doses, including with the aerosol formulation of loxapine [51]. No data on QT changes are available for fluphenazine, perphenazine, or trifluoperazine. No special cautions or monitoring are recommended for these drugs. Cardiac monitoring including ECG and potassium levels prior to starting one of these drugs is recommended only for patients with a history of cardiac disease.

Orthostatic hypotension — Orthostatic hypotension is most common with thioridazine and chlorpromazine among FGAs [52], occurring in clinical trials more often than with olanzapine [28] or loxapine [53]. Hypotension with chlorpromazine is particularly common when the drug is given parenterally. In contrast, changes in blood pressure are rarely reported with fluphenazine, haloperidol, or perphenazine. The most likely mechanism of orthostatic hypotension with FGAs is alpha-adrenergic blockade. 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. No specific monitoring has been recommended by manufacturers, but lower doses and slower titration may be appropriate for patients with signs of orthostatic changes.

Increased risk of mortality — Accumulating data from both observational studies and pooled analyses of randomized trials indicate that antipsychotic medications are associated with an increased risk of stroke, myocardial infarction, and death when used to treat behavioral symptoms in older adults with dementia [54-58]. The mechanism for this effect has not been firmly established. All antipsychotics prescribed in the United States carry a boxed warning from the FDA of a 1.6- to 1.7-fold increase in mortality from all causes for older adult patients with dementia-related psychosis [59].

Studies comparing the relative risk of various antipsychotics indicate that FGAs cause somewhat higher mortality than the SGAs [60-62]:

- A 2018 study of 6578 patients hospitalized following a myocardial infarction, which found an adjusted hazard ratio of 1.50 (95% CI 1.14-1.96) for a greater likelihood of death among patients receiving oral haloperidol compared with those given an SGA (7.8 versus 5.5 percent mortality rate in the seven days following admission) [63].

- A 2017 comparison of mortality rates in a cohort of 70,718 community-based patients with recently diagnosed Alzheimer disease in Finland similarly found a higher adjusted hazard ratio of 1.52 (95% CI 1.14-2.02) for haloperidol than for quetiapine (adjusted hazard ratio 0.84, 95% CI 0.75-0.94) [64].

No specific monitoring has been suggested to address mortality risk in general, but attention to cardiac and metabolic issues may be helpful, and alternatives to antipsychotic drugs should be used when possible, particularly for behavioral symptoms that are not severe and/or refractory. (See "Management of neuropsychiatric symptoms of dementia", section on 'Antipsychotic drugs'.)

Agranulocytosis — Rare but potentially fatal cases of agranulocytosis, neutropenia, and leukopenia have been reported with all FGAs. There is some evidence that drugs of the phenothiazine class (especially chlorpromazine, and to a lesser extent fluphenazine, perphenazine, thioridazine, and trifluoperazine) carry higher risk than other FGAs. The overall risk of agranulocytosis with these medications is 1 in 10,000 patients, whereas the risk for chlorpromazine is 0.13 percent [65]. For patients taking any FGA who either have previously experienced a drug-induced leukocytopenia or have a preexisting low white blood cell or absolute neutrophil count, monitoring is recommended during the first few months of treatment. A reasonable approach would be a white blood cell and absolute neutrophil count at baseline, after one to two weeks, and after three to six months.

Cholestatic jaundice — Chlorpromazine is associated with cholestatic jaundice in 1 to 2 percent of patients [66], usually occurring in the first month of treatment. A proposed mechanism for this effect is an inability of some patients to metabolize chlorpromazine via its usual primary pathway of sulfoxidation, allowing the formation of toxic metabolites via a secondary pathway involving hydroxylation [67]. Rare cases of jaundice have been reported with other FGAs and each carries a manufacturer's recommendation for annual liver function tests.

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 [68,69]. 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 FGAs, all 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.

Ocular — Pigmentary retinopathy (retinitis pigmentosa) and deposits in the lens or cornea leading to cataracts are the primary ocular issues reported with FGAs. Among these drugs, those chemically classified as phenothiazines (chlorpromazine, fluphenazine, perphenazine, thioridazine, and trifluoperazine) are generally found to carry the highest risk. Despite the differences in risk for ocular side effects, all FGAs carry the same manufacturers' recommendation for annual inquiry regarding visual problems and an ocular examination every two years in patients up to age 40 and annually thereafter.

Ocular issues specific to individual FGAs include:

- Thioridazine has most frequently been associated with pigmentary retinopathy [70-73]. Doses of thioridazine at or above 800 mg per day carry an especially high risk and the manufacturer accordingly recommends that doses be limited to 600 mg per day. A similar, but less frequent, pattern of risk at higher doses has been reported for chlorpromazine, fluphenazine, perphenazine, and trifluoperazine. Retinal problems have not been reported with haloperidol, loxapine, or pimozide. (See "Retinitis pigmentosa: Clinical presentation and diagnosis".)

- Evidence of corneal and lenticular deposits potentially leading to cataracts has been found in as many as one-third of patients taking chlorpromazine or thioridazine at high doses over long periods [73]. Fluphenazine, perphenazine, and trifluoperazine showed lower rates of the same phenomenon. As with retinal problems, haloperidol, loxapine, and pimozide have not been associated with these changes.

- Perphenazine has been associated with rare cases of epithelial keratopathies, mydriasis, myosis, and photophobia. The only issues associated with pimozide are photophobia and accommodation problems. Although worsening of narrow-angle glaucoma is theoretically possible with any anticholinergic medication, and all FGAs include a caution when used in these patients, a 2010 review found no reports of glaucoma with any of these medications [73].

Prolactin elevation — All FGAs have been shown to elevate prolactin levels, apparently through blockade of tuberoinfundibular dopamine, allowing uninhibited secretion of pituitary prolactin.

Both men and women taking FGAs typically have prolactin levels two to three times higher than normal and, although there is some evidence that patients may develop tolerance to this effect, the majority of patients continue to have elevated levels [74]. The clinical significance of excessive prolactin includes risk of menstrual irregularities, infertility, galactorrhea, loss of libido, and erectile and ejaculatory dysfunction. Patients on any FGA should be asked about sexual dysfunction and abnormal lactation annually, and a prolactin level should be included in the evaluation of these symptoms [47]. The relationship of elevated prolactin to the development of pituitary adenoma and the progression of breast cancer remains uncertain [74,75].

Sexual dysfunction — Even in the absence of prolactin elevation, all FGAs have been associated with impaired sexual function. A 2011 review concluded that more than 70 percent of patients on haloperidol experienced some form of sexual dysfunction [76]. A 2013 meta-analysis reported these symptoms in 45 percent of haloperidol- and 60 percent of thioridazine-treated patients [77]. In this study, the risk of any sexual dysfunction with haloperidol was only slightly greater than that reported for the SGAs risperidone and olanzapine, but the risk of arousal or orgasmic problems with thioridazine was twofold higher.

Sedation — The lower-potency FGAs chlorpromazine and thioridazine have high levels of histaminic H1 receptor antagonism and are highly sedating [17], a quality that sometimes leads to the use of chlorpromazine for sedation of severely agitated psychotic or delirious inpatients [78]. Outpatients receiving these drugs should be cautioned about driving or operating machinery. Chlorpromazine has been used in surgical, medical, and radiologic settings for conscious sedation with efficacy comparable to that of lorazepam [79]. The higher-potency drugs are significantly less sedating, especially fluphenazine, pimozide, thiothixene, and trifluoperazine [17].

Falls — Antipsychotic medications may cause falls and fractures as the result of somnolence, postural hypotension, and/or motor and sensory instability [80,81]. For patients with conditions or taking medications that could exacerbate these effects, the FDA recommended that a fall risk assessment be completed when initiating antipsychotic treatment and recurrently for patients continuing on long-term antipsychotics.

Seizure — A 2015 nested case-control analysis of over 60,000 patients from the United Kingdom found that the risk of seizure with FGAs was 49.4 per 10,000 person-years of exposure to chlorpromazine and thioridazine, and 59.1 for haloperidol and trifluoperazine, compared with 11.7 for control patients [82]. The increased seizure risk with FGAs is generally attributed to a lowering of seizure threshold rather than to new-onset problems. Manufacturer guidance for

each FGA cautions about use in patients at risk for seizures, including those taking other medications that lower seizure threshold.

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

- **Pharmacology** – The mechanism of action of first-generation antipsychotics (FGAs) appears to be postsynaptic blockade of brain dopamine D2 receptors. Aside from their common activity as D2 antagonists, each FGA has distinct effects on neuronal 5-HT2a, alpha-1, histaminic, and muscarinic receptors, which generally correspond to their individual side effect profiles, as shown in the table (table 1). (See 'Pharmacology' above.)

  - **Potency** – Pharmacological differences are the basis for classification of FGAs by potency. High-potency agents (eg, fluphenazine, haloperidol, perphenazine) have less sedation, less anticholinergic activity, and less weight gain but a higher risk for extrapyramidal symptoms (EPS) than low-potency agents (eg, chlorpromazine, thioridazine) (table 2). (See 'High- and low-potency FGAs' above.)

  - **Metabolism and drug interactions** – All FGAs undergo metabolism via the cytochrome P450 system. This makes the drugs susceptible to liver impairment and drug-drug interactions. The FGAs can interact with drugs that have potent effects on CYP metabolism, including the antidepressants fluoxetine, paroxetine, and bupropion, and the mood stabilizer carbamazepine. (See 'Metabolic activation and clearance' above.)

- **Preference for second-generation antipsychotics (SGAs)** – Due to the propensity of FGAs to cause EPS and tardive dyskinesia, SGAs are typically the preferred choice over FGAs in the treatment of psychosis. (See 'Administration' above.)

- **Side effects** – While antipsychotic medications are believed to be comparable in effectiveness (with the exception of clozapine for treatment-resistant schizophrenia), they differ in side effect profiles both individually and between FGAs and SGAs. Our choice of

antipsychotic is influenced by its side effect profile, and the patient's clinical status and risk factors. (See 'Side effects' above.)

- **Extrapyramidal symptoms** – These include rigidity, bradykinesia, tremor, and akathisia (restlessness). Among the FGAs, the high-potency drugs (eg, fluphenazine, haloperidol, pimozide, and thiothixene are usually associated with the highest risk of EPS) (table 1). (See 'Extrapyramidal symptoms' above.)

- **Tardive dyskinesia (TD)** – TD is characterized by involuntary choreoathetoid movements of the mouth, tongue, face, extremities, or trunk. TD risk increases with age, time of exposure to the medications, and prior development of EPS. TD has been reported with all FGAs at a cumulative rate of 5 percent per year, with higher risk in the older population. (See 'Tardive dyskinesia' above.)

- **Metabolic syndrome** – Weight gain, diabetes, dyslipidemia, diabetic ketoacidosis, and cardiovascular disease constitute a metabolic syndrome associated with antipsychotic medications (FGAs, SGAs). The potential morbidity of these symptoms has led to routine monitoring of weight, waist circumference, blood pressure, fasting glucose, and lipid profile of patients taking any of the antipsychotic medications (table 6). (See 'Metabolic syndrome' above.)

- **QT prolongation and sudden death** – Sudden death, believed in most cases to be caused by QT prolongation, has been reported with exposure to any antipsychotic medication. Chlorpromazine, thioridazine, and intravenous haloperidol are known to be the highest risk. We obtain an electrocardiogram and serum potassium level prior to the first dose of these agents.

- **Increased risk of mortality** – Accumulating data from both observational studies and pooled analyses of trials indicate that antipsychotic medications are associated with a 1.6- to 1.7-fold increased risk of stroke, myocardial infarction, and death when used to treat behavioral symptoms in older adults with dementia.

- **Neuroleptic malignant syndrome (NMS)** – NMS is a syndrome of fever, muscle rigidity, mental status changes, and autonomic instability, generally accompanied by rhabdomyolysis and creatine kinase elevation. The condition is rare but potentially fatal and constitutes a medical emergency. The physiological mechanism of NMS is unknown. (See "Neuroleptic malignant syndrome".)

- **Others** – Orthostatic hypotension, dry mouth, constipation, pigmentary retinopathy, sexual dysfunction, falls, seizures are seen less often, and rare cases of agranulocytosis

have been reported.

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