Advice to Patients

Importance of reading manufacturer's patient information.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs That Prolong QT Interval) or OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus).

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with ziprasidone, avoid driving, operating machinery, or performing hazardous tasks while taking ziprasidone until gain experience with the drug's effects.

Importance of taking medication exactly as prescribed by the clinician.

Importance of women informing clinicians immediately if they are or plan to become pregnant or plan to breast-feed.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview (see Users Guide). For additional information until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Ziprasidone Hydrochloride

Oral		
Capsules	20 mg	Geodon®, Pfizer
	40 mg	Geodon®, Pfizer
	60 mg	Geodon®, Pfizer
	80 mg	Geodon®, Pfizer

Ziprasidone Mesylate

Parenteral		
For Injection, for IM use only	20 mg (of ziprasidone)	Geodon®, Pfizer

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BUTYROPHENONES 28:16.08.08

Haloperidol

■ Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is considered a conventional or first-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Haloperidol is used for the symptomatic management of psychotic disorders. Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to improve symptoms between episodes and to minimize the risk of recurrent acute episodes. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Conventional antipsychotic agents, such as haloperidol, generally are considered to exhibit similar efficacy in treating acute psychotic symptoms, although they vary in their potency and adverse effect profile. Haloperidol is a high-potency antipsychotic that has been shown to be effective in the management of acute and stable phases of schizophrenia, but is frequently associated with extrapyramidal reactions such as akathisia, dystonia, or parkinsonian symptoms, even at low dosages.

Results of short-term studies indicate that haloperidol is more effective than placebo and equally or less effective than atypical antipsychotics in the treatment of positive (e.g., delusions, hallucinations) and negative symptoms (e.g., withdrawal from social interaction, blunted emotional expression) of schizophrenia. However, in one clinical study, haloperidol was less effective than the atypical antipsychotic agent risperidone in preventing relapse in adult outpatients with clinically active schizophrenia or schizoaffective disorders who were assigned to receive either drug for a minimum of 1 year. In this study, approximately 40% of patients in the study who received usual dosages of haloperidol had relapsed by the end of the study compared with approximately 25% of those receiving usual dosages of risperidone. Because atypical antipsychotics appear to be at least as effective in the treatment of positive symptoms and possibly more effective in the treatment of negative symptoms of schizophrenia and have fewer extrapyramidal reactions, some clinicians prefer use of atypical antipsychotics rather than conventional antipsychotics, such as haloperidol, for the management of schizophrenia, except in stable patients who have had good response to conventional antipsychotics without major adverse effects, in patients who require IM therapy, which is not yet available for some atypical antipsychotics, and for the acute management of aggression/violence in some patients, particularly those requiring long-acting (depot) parenteral preparations. However, patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

The long-acting decanoate ester of haloperidol is used parenterally principally in patients requiring prolonged antipsychotic therapy (e.g., patients with chronic schizophrenic disorder). Parenteral antipsychotic therapy with a long-acting preparation may be particularly useful in patients with a history of poor compliance. In addition, long-acting antipsychotic preparations may be useful in patients with suspected GI malabsorption or variable GI absorption of the drug. The principal disadvantage of long-acting parenteral antipsychotics is the inability to terminate the drug's action when severe adverse reactions occur. Long-acting antipsychotic preparations should not be used in the acute management of severely agitated patients. Generally, patients should be stabilized on antipsychotic medication prior to conversion to haloperidol decanoate therapy and should have previously received and tolerated a shorter-acting haloperidol preparation so that the possibility of an unexpected adverse reaction that potentially could not be readily reversed following the decanoate can be minimized. For further information on the use of antipsychotic agents in the symptomatic treatment of schizophrenia, see Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Tourette's Syndrome** Haloperidol is used for the control of tics and vocal utterances of Tourette's syndrome (Gilles de la Tourette's syndrome) in children and adults. Haloperidol generally has been considered the drug of choice for the management of Tourette's syndrome and pimozide has been be an effective alternative in some patients who have an inadequate response to or do not tolerate haloperidol. Because limited data suggest that pimozide may be more effective than haloperidol in reducing tics and pimozide appears to be better tolerated than haloperidol, some clinicians and experts prefer the use of pimozide in patients with Tourette's syndrome.

In children with tic disorders (e.g., Tourette's syndrome) and comorbid attention deficit hyperactivity disorder† (ADHD) in whom stimulants alone cannot control tics, haloperidol may be used concomitantly with a stimulant.

■ **Delirium** Antipsychotic agents, mainly haloperidol, have been used in the management of delirium†.

General Considerations Delirium is principally a disturbance of consciousness, attention, cognition, and perception but also may affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients, particularly hospitalized patients, and may be a harbinger of substantial morbidity and mortality.

Prevalence and Course The prevalence of delirium in hospitalized medically ill patients ranges from 10–30%; in those who are elderly, delirium ranges up to 40%. Up to 25% of hospitalized cancer patients and 30–40% of hospitalized patients with acquired immunodeficiency syndrome (AIDS) develop delirium. Up to about 50% of postoperative patients develop delirium, and up to 80% of terminally ill patients develop it near death. EEG abnormalities, mainly generalized slowing, have fairly good sensitivity for aiding in the diagnosis of delirium, but the absence of such changes does not rule out the diagnosis. Prodromal manifestations may progress to full-blown delirium over 1–3 days; the duration of delirium generally ranges from less than a week to more than 2 months, but typically does not exceed 10–12 days. Symptoms persist for up to 30 days or longer in up to 15% of patients, and frequently persist for longer than 1 month in geriatric patients. Although most patients recover fully, delirium may progress to stupor, coma, seizures, and death, particularly if untreated. Full recovery is less likely in geriatric patients and patients with AIDS, possibly because of underlying dementia in both populations.

Underlying general medical conditions associated with delirium include CNS disorders (e.g., head trauma, seizures, postictal state, vascular or degenerative disease), metabolic disorders (e.g., renal or hepatic failure, anemia, hypoxia, hypoglycemia, thiamine deficiency, endocrinopathy, fluid or electrolyte imbalance, acid-base imbalance), cardiopulmonary disorder (myocardial infarction, congestive heart failure, cardiac arrhythmia, shock, respiratory failure), and systemic illness (e.g., substance intoxication or withdrawal, infection, cancer, severe trauma, sensory deprivation, temperature dysregulation, postoperative state).

Management Overview. Clinicians should undertake an essential array of psychiatric management tasks designed to provide immediate interventions for urgent general medical conditions, identify and treat the etiology of delirium, ensure safety of the patient and others in contact with the patient, and improve the patient's functioning. Environmental (e.g., varying light levels in intensive care units to heighten awareness about time of day and reduce the perception of timelessness) and supportive interventions (e.g., to deal with disorientation, to assure the patient that manifestations are temporary and reversible and do not reflect a persistent psychiatric disorder) also generally are offered to patients with delirium† and are designed to reduce factors that may exacerbate delirium; to reorient patients, and to provide support. Patients may have life-threatening medical conditions that require therapeutic intervention

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even before a specific or definitive cause of the delirium is determined. The goal of diagnosis is to identify potentially reversible causes of delirium and prevent complications through prompt treatment of these specific disorders. Psychiatric management is essential and should be undertaken for all patients with delirium. Somatic interventions principally consist of drug therapy. The choice of somatic intervention will depend on the specific features of the patient's clinical condition, the underlying etiology of the delirium, and any associated comorbid conditions.

Drug Therapy. Antipsychotic agents often are the drugs of choice for the management of delirium†. Although other drugs (e.g., phenothiazines, droperidol) have been used, haloperidol generally is considered the antipsychotic of choice for most patients with delirium because of its relatively low risk of anticholinergic activity and of sedative and hypotensive effects. In addition, haloperidol has been studied most extensively, although few studies have used standardized definitions of delirium or reliable and valid delirium symptom rating measures to assess symptom severity before and after initiation of treatment. For drugs other than haloperidol, there have been no large, prospective studies that included a control. Evidence of efficacy for such alternative therapies, including second-generation antipsychotic agents (e.g., olanzapine, quetiapine, risperidone, ziprasidone), is principally from small case series, case reports, or open-label studies. In addition, interpretation of findings from many such case presentations is difficult because of use of nonstandardized delirium definitions and/or informal measures of delirium symptom severity. In general, evidence of the efficacy of antipsychotics, including haloperidol, in the management of delirium comes from numerous case reports and uncontrolled studies. However, evidence from a randomized, double-blind, comparator-drug controlled study (haloperidol, chlorpromazine, and lorazepam) in patients with AIDS that employed standardized clinical measures of delirium demonstrated clinical superiority of antipsychotic agents compared with benzodiazepines. Statistically significant improvement in the Delirium Rating Scale was evident after 2 days in patients receiving haloperidol or chlorpromazine but not in the lorazepam group (mean decreases in the score [i.e., improvement] were 8, 8.5, and 1, respectively). The symptomatic improvement in delirium occurred quickly among patients receiving antipsychotic therapy, usually before initiation of interventions directed at the medical etiologies of delirium.

Although various antipsychotic agents may be given orally, IM, or IV, IV administration is considered most effective in emergency situations or where oral access is limited. In addition, some evidence indicates that IV administration of antipsychotic agents may be associated with less severe extrapyramidal effects.

Special Precautions. Antipsychotic agents, particularly IV† haloperidol, used in the management of delirium have been associated with lengthening of the QT interval, possibly leading to atypical ventricular tachycardia (torsades de pointes), ventricular fibrillation, and sudden death. The manufacturer of Haldol® and the US Food and Drug Administration (FDA) state that although injectable haloperidol is approved *only* for IM injection and *not for IV administration*, there is considerable evidence from the medical literature that IV† administration of the drug is a relatively common, unlabeled ("off-label") clinical practice, principally for the treatment of severe agitation in intensive care units, and recommend ECG monitoring in any patient receiving the drug IV. Many clinicians also recommend that baseline and periodic or continuous ECG monitoring be performed with special attention paid to the length of the QT_c interval. Prolongation of the QT_c interval to greater than 450 msec or to greater than 15–25% over that in previous ECGs may warrant telemetry, a cardiology consultation, and dose reduction or discontinuance. Serum concentrations of magnesium and potassium also should be monitored at baseline and periodically in critically ill patients, especially those with baseline QT_c intervals of 440 msec or longer, those receiving other drugs known to increase the QT interval, and those who have electrolyte disorders. Limited evidence suggests that the incidence of torsades de pointes in patients receiving haloperidol IV is about 0.4–3.6%, but may increase to greater than 10% at relatively high IV doses (e.g., 35 mg or more over 24 hours). (See Cautions: Cardiovascular Effects and also see Cautions: Precautions and Contraindications.)

■ **Disruptive Behavior Disorder and Attention Deficit Hyperactivity Disorder** Haloperidol is used for the treatment of severe behavioral problems in children marked by combativeness and/or explosive hyperexcitable behavior (out of proportion to immediate provocations), and for the short-term treatment of hyperactive children who exhibit excessive motor activity with accompanying conduct disorders that are manifested as impulsive behavior, difficulty sustaining attention, aggression, mood lability, and/or poor frustration tolerance. However, the possible risks of tardive dyskinesia, withdrawal dyskinesia, and other extrapyramidal reactions should be considered. Some experts currently recommend use of haloperidol only for the treatment of comorbid tics in children with attention deficit hyperactivity disorder (ADHD). Some clinicians recommend routine administration of the Abnormal Involuntary Movement Scale (AIMS) to all children receiving antipsychotic agents.

■ **Nausea and Vomiting** Haloperidol also has been used in the prevention and control of severe nausea and vomiting† (e.g., cancer chemotherapy-induced emesis). Based on limited data, haloperidol appears to be as effective as phenothiazines in the prevention of cancer chemotherapy-induced emesis. Additional studies are required to determine the efficacy of haloperidol in the prevention and control of severe nausea and vomiting.

Dosage and Administration

■ **Administration** Haloperidol is administered orally. Haloperidol lactate is administered orally or by IM injection, and haloperidol decanoate is administered by IM injection. Pending accumulation of further data to establish safety and efficacy, IM administration of haloperidol lactate or decanoate in children is not recommended by the manufacturers. Haloperidol *lactate* also has been administered by IV injection† or infusion†. Haloperidol decanoate injection should *not* be administered IV.

Haloperidol decanoate should be administered by deep IM injection into the gluteal region using a 21-gauge needle. The manufacturers of haloperidol decanoate state that the maximum volume of haloperidol decanoate should not exceed 3 mL per IM injection site.

Haloperidol lactate and decanoate injections should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

■ **Dosage** Dosage of haloperidol lactate and the decanoate is expressed in terms of haloperidol.

There is considerable interindividual variation in optimum dosage requirements of haloperidol, and dosage must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage. Dosage should be increased more gradually in children and in debilitated, emaciated, or geriatric patients. Because of the risk of adverse reactions associated with cumulative effects of butyrophenones, patients with a history of long-term therapy with haloperidol and/or other antipsychotic agents should be evaluated periodically to determine whether maintenance dosage could be decreased or drug therapy discontinued.

Oral Dosage For the symptomatic management of psychotic disorders or Tourette's disorder in adults with moderate symptomatology and in geriatric or debilitated patients, the usual initial oral dosage of haloperidol is 0.5–2 mg 2 or 3 times daily. Subsequent dosage should be carefully adjusted according to the patient's tolerance and therapeutic response. Dosage during prolonged maintenance therapy should be kept at the lowest effective level.

The usual initial oral dosage of haloperidol for adults with severe symptomatology and/or chronic or resistant disorders is 3–5 mg 2 or 3 times daily. To achieve prompt control, higher dosages may be required in some patients. Patients who remain severely disturbed or inadequately controlled may require dosage adjustment. Oral dosages up to 100 mg daily may be required in some severely psychotic patients. Occasionally, dosages exceeding 100 mg daily have been used for the management of severely resistant disorders in adults; however, the safety of prolonged administration of such dosages has not been demonstrated.

The usual initial oral dosage of haloperidol in children 3–12 years of age and weighing 15–40 kg is 0.5 mg daily given in 2 or 3 divided doses. Subsequent dosage may be increased by 0.5 mg daily at 5- to 7-day intervals, depending on the patient's tolerance and therapeutic response.

For the symptomatic management of psychotic disorders in children 3–12 years of age, the usual oral dosage range is 0.05–0.15 mg/kg daily given in 2 or 3 divided doses; however, severely disturbed psychotic children may require higher dosages. Dosage during prolonged maintenance therapy should be kept at the lowest possible effective level; once an adequate response has been achieved, dosage should be gradually reduced and subsequently adjusted according to the patient's therapeutic response and tolerance.

For the management of non-psychotic behavioral problems and for the control of Tourette's disorder in children 3–12 years of age, the usual oral dosage range is 0.05–0.075 mg/kg daily given in 2 or 3 divided doses. Unlike psychotic disorders for which prolonged therapy is usually required, non-psychotic or hyperactive behavioral problems in children may be acute, and short-term administration of haloperidol may be adequate. A maximum effective dosage of haloperidol for the management of behavioral problems in children has not been established; however, the manufacturers state that there is little evidence that improvement in behavior is further enhanced at dosages greater than 6 mg daily.

IM Dosage For the prompt control of acutely agitated patients with moderately severe to very severe symptoms, the usual initial adult IM dose of haloperidol lactate is 2–5 mg (of haloperidol) given as a single dose. Depending on the response of the patient, this dose may be repeated as often as every hour; however, IM administration of haloperidol lactate every 4–8 hours may be adequate to control symptoms in some patients.

Oral therapy should replace short-acting parenteral therapy as soon as possible. Depending on the patient's clinical status, the first oral dose should be given within 12–24 hours following administration of the last parenteral dose of haloperidol lactate. Since bioavailability studies to establish bioequivalence between oral and parenteral dosage forms of haloperidol have not been conducted to date, the manufacturers suggest that the parenteral dosage administered during the preceding 24 hours be used for initial approximation of the total daily oral dosage required. Since this dosage is only an initial estimate, patients being switched from parenteral haloperidol lactate therapy to oral therapy should be closely monitored, particularly for clinical signs and symptoms of efficacy; sedation, and adverse effects, for the first several days following initiation of oral therapy. Subsequent dosage may be increased or decreased according to the patient's tolerance and therapeutic response, using the lowest possible effective dosage.

For patients requiring prolonged antipsychotic therapy (e.g., patients with

chronic schizophrenic disorder), the long-acting haloperidol decanoate injection may be considered. If the decanoate is used, the patient's condition should initially be stabilized with an antipsychotic agent prior to attempting conversion to haloperidol decanoate. In addition, if the patient is receiving an antipsychotic agent other than haloperidol, it is recommended that the patient initially be converted to oral haloperidol therapy in order to minimize the risk of an unexpected adverse reaction to the drug, which might not be readily reversible following use of the decanoate.

The initial IM dose of haloperidol decanoate should be based on the patient's clinical history, physical condition, and response to previous antipsychotic therapy. To determine the minimum effective dosage, haloperidol decanoate therapy has been initiated at low initial doses and gradually titrated upward as necessary. A precise formula for converting from oral haloperidol dosage to IM haloperidol decanoate has not been established, but an initial adult dose 10–20 times the previous daily dose of oral haloperidol, not exceeding 100 mg (regardless of previous antipsychotic dosage requirements), is suggested, although limited clinical experience suggests that a lower initial dosage of the decanoate may be adequate. If conversion requires an initial dosage of haloperidol decanoate higher than 100 mg daily, such dosage should be administered in 2 injections (i.e., administering a maximum initial dose of 100 mg followed by the balance in 3–7 days). However, some clinicians have converted therapy to the decanoate using a higher initial dosage.

IM haloperidol decanoate usually has been administered at monthly intervals (i.e., every 4 weeks), but individual response may dictate the need for adjusting the dosing interval as well as the dose.

Lower initial dosages (e.g., 10–15 times the previous daily dose of oral haloperidol) and more gradual upward titration are recommended for patients who are geriatric, debilitated, or stabilized on low oral dosages.

Close clinical observation is required during dosage titration in order to minimize the risk of overdosage and of emergence of psychotic manifestations prior to the next dose. If supplemental antipsychotic therapy is necessary during periods of dosage titration or for control of acute exacerbations of psychotic manifestations, a short-acting haloperidol preparation should be used. Experience with haloperidol decanoate dosages exceeding 450 mg (of haloperidol) monthly is limited.

IV Dosage The optimum dosage of haloperidol for the treatment of delirium has not been established. However, initiation of IV† haloperidol with dosages of 1–2 mg every 2–4 hours in adults has been suggested. Lower IV dosages (e.g., 0.25–0.5 mg every 4 hours) have been suggested for geriatric patients with delirium; severely agitated adults may require titration to higher dosages. Although single IV doses up to 50 mg or total daily dosages of 500 mg have been reported in adults, the risk of adverse effects, particularly prolongation of the QT interval and torsades de pointes, must be considered. (See Uses: Delirium and see also Cautions: Cardiovascular Effects and Cautions: Precautions and Contraindications.) Some evidence suggests that the risk of torsades de pointes increases at total daily dosages of 35–50 mg or more. In patients requiring multiple IV injections of the drug to control delirium (e.g., more than eight 10-mg doses in 24 hours or more than 10 mg/hour for more than 5 consecutive hours), consideration can be given to continuous IV infusion† of haloperidol; in such patients, an initial 10-mg dose followed by an infusion of 5–10 mg/hour has been suggested. If agitation persists, repeat 10-mg IV doses at 30-minute intervals, accompanied by a 5 mg/hour increase in the infusion rate, can be considered. ECG should be determined at baseline and periodically or continuously thereafter, with special attention paid to possible prolongation of the QT interval, and dosage should be reduced or the drug discontinued if clinically important QT prolongation (e.g., 15–25% or more over baseline) occurs or the QT_c exceeds 450 msec. (See Uses: Delirium and see also Cautions: Cardiovascular Effects and Cautions: Precautions and Contraindications.)

Cautions

Haloperidol shares the toxic potentials of phenothiazines, and the usual precautions of phenothiazine therapy should be observed. The total incidence of adverse effects associated with haloperidol is similar to that associated with piperazine-derivative phenothiazines. (See Cautions in the Phenothiazines General Statement 28:16.08.24.)

Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of mortality. (See Cautions: Geriatric Precautions.)

■ **Nervous System Effects** The most frequent adverse effects of haloperidol involve the CNS.

Extrapyramidal Reactions Extrapyramidal reactions occur frequently with haloperidol, especially during the first few days of therapy. In most patients, these reactions consist of parkinsonian symptoms (e.g., marked drowsiness and lethargy, drooling or hypersalivation, fixed stare), which are mild to moderate in severity and are usually reversible following discontinuance of the drug. Other adverse neuromuscular reactions have been reported less frequently, but are often more severe, and include feelings of motor restlessness (i.e., akathisia), tardive dystonia, and dystonic reactions (e.g., hyperreflexia, opisthotonos, oculogyric crisis, torticollis, trismus). Generally, the occurrence and severity of most extrapyramidal reactions are dose related, since they occur at relatively high dosages and disappear or become less severe following a reduction in dosage; however, severe extrapyramidal reactions have reportedly occurred at relatively low dosages. Most patients respond rapidly to treatment with an anticholinergic antiparkinsonian drug (e.g., benztropine, trihexyphenidyl). If persistent extrapyramidal reactions occur, haloperidol therapy may have to be discontinued.

Neuroleptic malignant syndrome (NMS) may occur in patients receiving haloperidol or other antipsychotic therapy. NMS is potentially fatal and requires immediate discontinuance of the drug and initiation of intensive symptomatic and supportive care. For additional information on NMS, see Extrapyramidal Reactions in Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia Like other antipsychotic agents (e.g., phenothiazines), haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia may occur in some patients during long-term administration of haloperidol or it may occur following discontinuance of the drug. The risk of developing tardive dyskinesia appears to be greater in geriatric patients receiving high dosages of the drug, especially females. The symptoms are persistent, and in some patients appear to be irreversible. Tardive dyskinesia is characterized by rhythmic involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of the tongue, puffing of cheeks, chewing movements, puckering of the mouth), which sometimes may be accompanied by involuntary movements of the extremities and/or trunk. Although not clearly established, the risk of developing the syndrome and the likelihood that it will become irreversible may increase with the duration of therapy and total cumulative dose of antipsychotic agent(s) administered; however, the syndrome may occur, although much less frequently, after relatively short periods of treatment with low dosages. There is no proven or uniformly effective treatment for tardive dyskinesia; antiparkinsonian agents do not alleviate and tend to exacerbate the symptoms of this syndrome. If possible, antipsychotic agents should be discontinued if signs or symptoms of tardive dyskinesia occur. The syndrome may partially or completely remit if antipsychotic agents are discontinued, although some patients may require many months for improvement. Tardive dyskinesia may be masked if therapy is reinstituted, dosage is increased, or therapy with another antipsychotic agent is initiated. The effect that masking of the symptoms may have on the long-term course of the syndrome is not known. Fine vermicular movement of the tongue may be an early sign of the syndrome; prompt discontinuance of haloperidol after this sign occurs may prevent development of the syndrome.

In general, abrupt withdrawal of antipsychotic agents following short-term administration is not associated with adverse effects; however, transient dyskinetic signs have occurred following abrupt withdrawal in patients receiving prolonged maintenance therapy with haloperidol. In some patients, the dyskinetic movements are indistinguishable, except on the basis of their duration, from tardive dyskinesia. It is not known whether gradual withdrawal of antipsychotic agents reduces the incidence of withdrawal-emergent neurologic signs; however, if haloperidol therapy must be discontinued, gradual withdrawal of the drug is recommended, if possible, pending further accumulation of data.

Other Nervous System Effects Tardive dystonia, not associated with tardive dyskinesia, has occurred in patients receiving haloperidol. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements; often is persistent, and potentially can become irreversible.

Other adverse nervous system effects of haloperidol include insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, and tonic-clonic seizures. Exacerbation of psychotic symptoms (including hallucinations and catatonic-like behavior), which may subside following discontinuance of therapy or treatment with anticholinergic agents, has also been reported.

Adverse anticholinergic effects of haloperidol include dry mouth (xerostomia), blurred vision, constipation, urinary retention, and diaphoresis. Priapism has also occurred.

■ **Hematologic Effects** Mild and usually transient leukopenia/neutropenia and leukocytosis have been reported in patients receiving antipsychotic agents, including haloperidol. Agranulocytosis (including fatal cases) has also been reported rarely in patients receiving haloperidol, but only when combined with other drugs. Possible risk factors for leukopenia and neutropenia include preexisting low leukocyte count and a history of drug-induced leukopenia or neutropenia. (See Cautions: Precautions and Contraindications.) Other adverse hematologic effects associated with haloperidol include anemia, minimal decreases in erythrocyte count, and a tendency toward lymphomonocytosis.

■ **Endocrine and Metabolic Effects** Moderate engorgement of the breast with lactation has occurred in some females receiving haloperidol. Galactorrhea, mastalgia, gynecomastia, increased libido, impotence, hyperglycemia, hypoglycemia, and hyponatremia have also occurred in some patients. Antipsychotic agents increase serum prolactin concentrations. (See Cautions: Mutagenicity and Carcinogenicity.) Although not reported to date with haloperidol, the manufacturers caution that decreases in serum cholesterol concentration have occurred in patients receiving chemically related drugs.

■ **Cardiovascular Effects** Tachycardia, hypotension, hypertension, ECG changes (including those compatible with QT-interval prolongation and the polymorphous configuration of torsades de pointes), and sudden death have been reported in patients receiving haloperidol. The US Food and Drug Administration (FDA) states that there have been at least 28 case reports of QT-interval prolongation and torsades de pointes, including some that were fatal, in patients receiving the drug IV†. In addition, FDA states that case-control

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studies have demonstrated a dose-dependent relationship between IV haloperidol dosage and subsequent development of torsades de pointes. A postmarketing analysis of a worldwide safety database revealed 229 reports of QT-interval prolongation and torsades de pointes with oral or parenteral haloperidol; many of these cases were confounded by concomitant administration of drugs known to prolong the QT interval or medical conditions associated with QT-interval prolongation. The reports included 73 cases of torsades de pointes, 11 of which were fatal. In 8 out of 11 fatal cases, haloperidol was administered IV in various dosages. In another postmarketing analysis of adverse cardiovascular events associated with haloperidol decanoate, 13 cases of torsades de pointes, QT-interval prolongation, ventricular arrhythmias, and/or sudden death were identified.

FDA states that it is not possible to estimate the frequency with which QT-interval prolongation or torsades de pointes occurs following administration of haloperidol based on these case reports alone. However, use of higher than recommended doses of any haloperidol formulation and IV administration of the drug appear to be associated with an increased risk of these effects. Many of the reported cases of QT-interval prolongation and torsades de pointes have occurred in patients receiving relatively high dosages of IV haloperidol (e.g., exceeding 35 mg daily); however, such effects also have been reported in patients receiving lower IV dosages or oral therapy. Although cases of sudden death, torsades de pointes, and QT-interval prolongation have been reported even in the absence of predisposing factors, FDA, the manufacturer of Haldol®, and some clinicians state that particular caution is advised when using any formulation of haloperidol in patients who have other QT-interval prolonging conditions, including electrolyte imbalance (particularly hypokalemia and hypomagnesemia), underlying cardiac abnormalities, hypothyroidism, or familial long QT syndrome, or those who are concomitantly taking medications known to prolong the QT interval. (See Uses: Delirium, Cautions: Precautions and Contraindications, and Acute Toxicity: Manifestations.) FDA states that clinicians should consider this new cardiovascular risk information when making individual treatment decisions for their patients.

Cases of sudden and unexpected death have been reported in haloperidol-treated patients. The nature of the evidence makes it impossible to determine definitively what role, if any, haloperidol played in the outcome of the cases reported to date. Although the possibility that haloperidol played a causative role in these deaths cannot be excluded, it should be kept in mind that sudden and unexpected death may occur in psychotic patients when they remain untreated or when they are treated with other antipsychotic medications.

■ **Other Adverse Effects** Impaired liver function and/or jaundice, maculopapular and acneiform dermatologic reactions, photosensitivity, alopecia, anorexia, diarrhea, hypersalivation, dyspepsia, nausea, vomiting, cataracts, retinopathy, and visual disturbances have also been reported.

Hyperpyrexia and heat stroke, not associated with neuroleptic malignant syndrome (see Extrapyramidal Reactions in Cautions: Nervous System Effects), have been reported in some patients receiving haloperidol.

Laryngospasm, bronchospasm, and increased depth of respiration have occurred in patients receiving haloperidol. Bronchopneumonia, resulting in fatalities in some patients, has occurred following the use of antipsychotic agents, including haloperidol. It has been suggested that lethargy and decreased thirst, resulting from central inhibition, may cause dehydration, hemoconcentration, and reduced pulmonary ventilation.

Hyperammonemia following haloperidol treatment has been reported in at least one child with citrullinemia, an inherited disorder of ammonia excretion.

■ **Precautions and Contraindications** Haloperidol shares the toxic potentials of other antipsychotic agents (e.g., phenothiazines), and the usual precautions associated with therapy with these agents should be observed. (See Cautions in the Phenothiazines General Statement 28:16.08.24.)

Geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of mortality. (See Cautions: Geriatric Precautions.)

Patients should be warned that haloperidol may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Patients also should be warned that haloperidol may enhance their response to alcohol, barbiturates, or other CNS depressants.

Because of the possibility of transient hypotension and/or precipitation of angina, haloperidol should be used with caution in patients with severe cardiovascular disorders. If hypotension occurs, metaraminol, norepinephrine, or phenylephrine may be used; epinephrine should *not* be used since haloperidol causes a reversal of epinephrine's vasopressor effects and a further lowering of blood pressure.

Since haloperidol may lower the seizure threshold, the drug should be used with caution in patients receiving anticonvulsant agents and in those with a history of seizures or EEG abnormalities. Adequate anticonvulsant therapy should be maintained during administration of haloperidol.

The manufacturers state that haloperidol should be used with caution in patients with known allergies or with a history of allergic reactions to drugs.

When concomitant therapy with an antiparkinsonian drug is necessary to manage haloperidol-induced extrapyramidal symptoms, it may be necessary to continue the antiparkinsonian drug for a period of time after discontinuance of haloperidol in order to prevent emergence of these symptoms.

The manufacturers caution that when haloperidol is used to control mania in patients with bipolar disorder, there may be a rapid mood swing to depression.

Haloperidol should be used with caution in patients with thyrotoxicosis since severe neurotoxicity (e.g., rigidity, inability to walk or talk) may occur in these patients during therapy with an antipsychotic agent.

Cases of leukopenia and neutropenia have been reported in patients receiving antipsychotic agents, including haloperidol; agranulocytosis (including fatal cases) has also been reported. (See Cautions: Hematologic Effects.) Patients with a preexisting low leukocyte count or a history of drug-induced leukopenia or neutropenia should have their complete blood count monitored frequently during the first few months of therapy and haloperidol should be discontinued at the first sign of a decline in the leukocyte count in the absence of other causative factors. Haloperidol-treated patients with neutropenia should be carefully monitored for fever or other signs or symptoms of infection and be treated promptly should such signs and symptoms occur. Patients with severe neutropenia (absolute neutrophil count less than 1000/mm^3) should discontinue haloperidol and have their leukocyte count followed until recovery.

Care should be taken to avoid skin contact with haloperidol lactate oral solution and injection, since contact dermatitis has occurred rarely.

Cases of sudden death, QT-interval prolongation, and torsades de pointes have been reported in patients receiving haloperidol. (See Uses: Delirium and see also Cautions: Cardiovascular Effects.) Use of higher than recommended doses of any haloperidol formulation and IV† administration of the drug appear to be associated with an increased risk of QT-interval prolongation and torsades de pointes. Although these effects have been reported in the absence of predisposing factors, haloperidol should be used with particular caution in patients with other conditions that prolong the QT interval, including electrolyte imbalance (particularly hypokalemia and hypomagnesemia), underlying cardiac abnormalities, hypothyroidism; and familial long QT syndrome, as well as in those concurrently receiving other drugs known to prolong the QT interval. In addition, ECG monitoring is recommended whenever haloperidol is administered IV. (See Uses: Delirium.)

Haloperidol is contraindicated in patients with severe toxic CNS depression or in those who are comatose from any cause. Haloperidol also is contraindicated in patients who are hypersensitive to the drug and in those with parkinsonian syndrome.

■ **Pediatric Precautions** Safety and efficacy of haloperidol decanoate injection in children have not been established, and safety and efficacy of other haloperidol preparations in children younger than 3 years of age have not been established. Hyperammonemia was reported during postmarketing surveillance in a 5.5-year-old child with citrullinemia, an inherited disorder of ammonia excretion, following haloperidol therapy.

■ **Geriatric Precautions** Clinical studies of haloperidol did not include sufficient numbers of geriatric patients 65 years of age and older to determine whether this age group responds differently from younger adults. Other reported clinical experience has not consistently identified differences in responses between geriatric and younger patients. However, the prevalence of tardive dyskinesia appears to be highest among geriatric patients, particularly elderly women. In addition, the pharmacokinetics of haloperidol generally warrant the use of reduced dosages in geriatric patients. (See Dosage and Administration: Dosage.)

Geriatric patients with dementia-related psychosis treated with either conventional or atypical antipsychotic agents are at an increased risk of mortality. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in geriatric patients mainly receiving atypical antipsychotic agents revealed an approximate 1.6- to 1.7-fold increase in mortality compared with that in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in those receiving placebo. Although the causes of death were varied in these trials, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Subsequently, 2 observational, epidemiologic studies have indicated that, similar to atypical antipsychotic agents, treatment with conventional antipsychotic agents may increase mortality; the causes of death were not reported in the first study, and cancer and cardiac disease were the causes of death with the highest relative risk in the second study. However, the extent to which these findings of increased mortality in observational studies may be attributed to the antipsychotic agent as opposed to certain patient characteristics remains unclear.

The US Food and Drug Administration (FDA) currently advises clinicians that antipsychotic agents, including haloperidol, are *not* approved for the treatment of dementia-related psychosis. The FDA further advises clinicians that no drugs currently are approved for the treatment of dementia-associated psychosis and that other management options should be considered in patients with this disorder. The decision whether to prescribe antipsychotic agents "off-label" in the treatment of dementia symptoms is left to the discretion of the clinician. Clinicians who prescribe antipsychotic agents for geriatric patients with dementia-related psychosis should discuss the increased mortality risk with patients, their families, and their caregivers. In addition, patients currently receiving antipsychotic agents for dementia-associated symptoms should not abruptly stop taking the drugs; caregivers and patients should discuss any possible concerns with their clinician. For additional information on the use of antipsychotic agents for dementia-associated psychosis and other behavioral disturbances, see Geriatric Considerations under Psychotic Disorders: Schizophrenia and Other Psychotic Disorders, in Uses and see also Cautions: Geriatric Precautions, in the Phenothiazines General Statement 28:16.08.24.

■ **Mutagenicity and Carcinogenicity** Negative or inconsistent positive findings have been reported in vitro and in vivo in studies on the effects of conventional preparations of haloperidol on chromosome structure and number. However, the available cytogenetic evidence is considered too inconsistent to be conclusive at this time.

Although an increase in mammary neoplasms has been found in rodents following long-term administration of prolactin-stimulating antipsychotic agents, no clinical or epidemiologic studies conducted to date have shown an association between long-term administration of these drugs and mammary tumorigenesis in humans. Current evidence is considered too limited to be conclusive, and further study is needed to determine the clinical importance in most patients of elevated serum prolactin concentrations associated with antipsychotic agents. Since in vitro tests indicate that approximately one-third of human breast cancers are prolactin dependent, haloperidol should be used with caution in patients with previously detected breast cancer.

■ **Pregnancy, Fertility, and Lactation** Although there are no adequate and controlled studies to date in humans, 2 cases of limb malformations (e.g., phocomelia) have occurred in offspring of women who were given haloperidol concurrently with other potentially teratogenic drugs during the first trimester of pregnancy; these teratogenic effects have not been directly attributed to haloperidol. Haloperidol has been shown to be teratogenic and fetotoxic in animals at dosages 2–20 times the usual maximum human dosage. Haloperidol should be used during pregnancy or in women likely to become pregnant only when the potential benefits justify the possible risks to the fetus.

The effect of haloperidol on fertility in humans is not known. Impotence, increased libido, priapism, and menstrual irregularities have occurred in some individuals during haloperidol therapy.

Haloperidol is distributed into milk. The manufacturers warn that nursing should not be undertaken by women receiving haloperidol.

Drug Interactions

■ **CNS Depressants** Haloperidol may be additive with, or may potentiate the action of, other CNS depressants such as opiates or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol. When haloperidol is used concomitantly with other CNS depressants, caution should be used to avoid excessive sedation.

■ **Lithium** Although most patients receiving lithium and an antipsychotic agent (e.g., haloperidol, phenothiazines) concurrently do not develop unusual adverse effects, an acute encephalopathic syndrome occasionally has occurred, especially when high serum lithium concentrations were present. Patients receiving such combined therapy should be observed for evidence of adverse neurologic effects; treatment should be promptly discontinued if such signs or symptoms appear. (See Drug Interactions: Antipsychotic Agents, in the monograph on Lithium Salts 28:28.)

■ **Anticoagulants** Haloperidol has been reported to antagonize the anticoagulant activity of phenindione in one patient. Further study is needed to determine the clinical importance of this interaction.

■ **Rifampin** Concomitant oral therapy with rifampin and haloperidol in schizophrenic patients resulted in a mean 70% decrease in plasma haloperidol concentrations and decreased antipsychotic efficacy. Following discontinuance of rifampin in other schizophrenic patients treated with oral haloperidol, mean haloperidol concentrations increased 3.3-fold. Careful monitoring of clinical status and appropriate dosage adjustment are warranted whenever rifampin is initiated or discontinued in patients stabilized on haloperidol.

■ **Drugs with Anticholinergic Effects** The manufacturers caution that increases in intraocular pressure may occur in patients receiving anticholinergic drugs, including antiparkinsonian agents, concurrently with haloperidol.

■ **Drugs that Prolong QT Interval** Cases of QT-interval prolongation and torsades de pointes have been reported in patients receiving haloperidol. Patients receiving higher than recommended dosages of any haloperidol preparation and those receiving the drug IV appear to be at a higher risk of developing these adverse effects. Particular caution is advised when oral or parenteral haloperidol is used in patients concurrently receiving other drugs that prolong the QT interval.

■ **Methyldopa** Dementia has reportedly occurred in several patients who received haloperidol and methyldopa concomitantly. Although the clinical importance of this possible interaction has not been determined, patients should be carefully observed for adverse psychiatric symptoms if the drugs are used concurrently.

Acute Toxicity

■ **Manifestations** In general, overdosage of haloperidol may be expected to produce effects that are extensions of common adverse reactions; severe extrapyramidal reactions, hypotension, and sedation have been the principal effects reported. Coma with respiratory depression and hypotension (sometimes shock-like) may occur.

Substantial prolongation of the QT interval and atypical ventricular tachycardia (torsades de pointes) have occurred following haloperidol overdosage. The possibility of ECG changes associated with torsades de pointes should be considered following haloperidol overdosage, and ECG and vital signs should be monitored for signs of QT prolongation or dysrhythmias, continuing such monitoring until the ECG is normal.

Following accidental overdosage in a 2-year-old child, hypertension, rather than hypotension, reportedly occurred. Extrapyramidal reactions may consist of muscular weakness or rigidity and a generalized or localized tremor. Manifestations of overdosage with haloperidol decanoate injection may be prolonged.

■ **Treatment** Treatment of haloperidol overdosage generally involves symptomatic and supportive care. There is no specific antidote for haloperidol intoxication; however, anticholinergic or antiparkinsonian drugs may be useful in controlling extrapyramidal reactions associated with haloperidol overdosage.

Following acute ingestion of the drug, the stomach should be emptied by inducing emesis or by gastric lavage. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Activated charcoal should be administered after gastric lavage and/or emesis.

ECG and vital signs should be monitored, particularly for signs of QT prolongation or dysrhythmias. Severe arrhythmias should be treated with appropriate antiarrhythmic measures. Appropriate therapy should be instituted if hypotension or excessive sedation occurs; epinephrine should *not* be used (see Cautions: Precautions and Contraindications).

Pharmacology

The principal pharmacologic effects of haloperidol are similar to those of piperazine-derivative phenothiazines. The precise mechanism of antipsychotic action of haloperidol is unclear, but the drug appears to depress the CNS at the subcortical level of the brain, midbrain, and brain stem reticular formation. Haloperidol appears to inhibit the ascending reticular activating system of the brain stem (possibly through the caudate nucleus), thereby interrupting the impulse between the diencephalon and the cortex. The drug may antagonize the actions of glutamic acid within the extrapyramidal system. Inhibition of catecholamine receptors may also be important in the mode of action of haloperidol; the drug may also inhibit the reuptake of various neurotransmitters in the midbrain. Haloperidol appears to have strong central antidopaminergic and weak central anticholinergic activity. Like phenothiazines, haloperidol produces catalepsy and inhibits spontaneous motor activity and conditioned avoidance behaviors in animals. Haloperidol inhibits the central and peripheral effects of apomorphine, produces ganglionic blockade, and reduces affective responses. The precise mechanism of antiemetic action of haloperidol is unclear, but like some phenothiazines (e.g., chlorpromazine, prochlorperazine), haloperidol has been shown to directly affect the chemoreceptor trigger zone (CTZ), apparently by blocking dopamine receptors in the CTZ.

Like other dopamine receptor antagonists (e.g., phenothiazines), haloperidol may cause extrapyramidal reactions, and there appears to be a very narrow range between the effective therapeutic dosage for the management of acute psychotic disorders and that causing extrapyramidal symptoms.

Haloperidol produces less sedation, hypotension, and hypothermia than chlorpromazine.

Pharmacokinetics

■ **Absorption** Haloperidol is well absorbed from the GI tract following oral administration, but appears to undergo first-pass metabolism in the liver. Oral bioavailability of the drug has been reported to average 60%. The drug may undergo some enterohepatic circulation. Peak plasma concentrations of haloperidol occur within 2–6 hours following oral administration. Following IM administration of haloperidol lactate, peak plasma haloperidol concentrations occur within 10–20 minutes and peak pharmacologic action occurs within 30–45 minutes; in acutely agitated patients, control of psychotic manifestations may become apparent within 30–60 minutes, with substantial improvement often occurring within 2–3 hours. Haloperidol concentrations are detectable in plasma for several weeks following administration of a single dose of the drug.

Esterification of haloperidol results in slow and gradual release of haloperidol decanoate from fatty tissues, thus prolonging the duration of action; administration of the ester in a sesame oil vehicle further delays the rate of release. Following IM administration of haloperidol decanoate, plasma haloperidol concentrations are usually evident within 1 day and peak concentrations generally occur within about 6–7 days (range: 1–9 days). Steady-state plasma haloperidol concentrations are usually reached in approximately 3 months following once-monthly IM injection of the decanoate. In one group of patients receiving 20–400 mg monthly, data adjusted to 100-mg monthly doses suggested mean trough plasma haloperidol concentrations of 2 ng/mL after the first dose and of 4 ng/mL at steady state; accumulation during 24 months of therapy was not apparent. Within the usual dosage range, plasma haloperidol concentrations following IM administration of the decanoate are approximately proportional and linearly related to dosage; however, there is considerable interindividual and intraindividual variation in plasma concentrations attained with a given dosage.

■ **Distribution** Distribution of haloperidol into human body tissues and fluids has not been fully characterized. Following administration of haloperidol in animals, the drug is distributed mainly into the liver, with lower concentrations being distributed into the brain, lungs, kidneys, spleen, and heart.

Haloperidol is about 92% bound to plasma proteins.

Haloperidol is distributed into milk.

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■ **Elimination** Although the exact metabolic fate has not been clearly established, it appears that haloperidol is principally metabolized in the liver. The drug appears to be metabolized principally by oxidative *N*-dealkylation of the piperidine nitrogen to form fluorophenylcarbonic acids and piperidine metabolites (which appear to be inactive), and by reduction of the butyrophenone carbonyl to the carbinol, forming hydroxyhaloperidol. Limited data suggest that the reduced metabolite, hydroxyhaloperidol, has some pharmacologic activity, although its activity appears to be less than that of haloperidol. Urinary metabolites in rats include *p*-fluorophenaceturic acid, *β*-*p*-fluorobenzoylpropionic acid, and several unidentified acids.

Haloperidol and its metabolites are excreted slowly in urine and feces. Approximately 40% of a single oral dose of haloperidol is excreted in urine within 5 days. About 15% of an oral dose of the drug is excreted in feces via biliary elimination. Small amounts of the drug are excreted for about 28 days following oral administration.

Following IM administration of haloperidol decanoate, the esterified compound is initially distributed into fatty tissue stores, from which the drug is then slowly and gradually released and subsequently undergoes hydrolysis by plasma and/or tissue esterases to form haloperidol and decanoic acid. Subsequent distribution, metabolism, and excretion of haloperidol appears to be similar to those of orally administered drug. Following IM administration of the decanoate, the drug has an apparent half-life of approximately 3 weeks.

Chemistry and Stability

■ **Chemistry** Haloperidol is a butyrophenone-derivative antipsychotic agent. The drug is structurally similar to droperidol. Haloperidol is commercially available as the base, decanoic acid ester (decanoate), and lactate salt.

Haloperidol occurs as a white to faintly yellowish, amorphous or microcrystalline powder and has solubilities of less than 0.1 mg/mL in water and of approximately 16.7 mg/mL in alcohol at 25°C. The drug has a pK_a of 8.3.

Haloperidol decanoate occurs as a clear, light amber, oily liquid and is soluble in fixed oils (e.g., sesame oil) and in most organic solvents. The decanoate has a solubility of approximately 0.01 mg/mL in water. Haloperidol decanoate injection is commercially available as a sterile solution of the drug in sesame oil and contains benzyl alcohol as a preservative.

Haloperidol injection is prepared with the aid of lactic acid and contains the drug as the lactate salt; the injection is a sterile solution of the drug in water for injection. Commercially available injections are adjusted to pH 3–3.8 with lactic acid and also *may* contain parabens as preservatives. Haloperidol oral solution also is prepared with the aid of lactic acid and contains the drug as the lactate salt. The commercially available oral solution has a pH of 2.75–3.75.

■ **Stability** Commercially available haloperidol preparations should be stored in tight, light-resistant containers at controlled room temperature between 15–30°C; freezing of the oral solution and injections and refrigeration of the decanoate injection should be avoided.

Haloperidol lactate injection may be compatible with some drugs for a short period of time after mixing, but at least one manufacturer recommends that the lactate not be mixed with other drugs. Haloperidol decanoate injection is incompatible with sterile water for injection or sodium chloride injection and with other aqueous injections. Specialized references should be consulted for specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Haloperidol

Oral		
Tablets	0.5 mg*	Haloperidol Tablets
	1 mg*	Haloperidol Tablets
	2 mg*	Haloperidol Tablets
	5 mg*	
	10 mg*	Haloperidol Tablets
		Haloperidol Tablets
	20 mg*	Haloperidol Tablets

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Haloperidol Decanoate

Parenteral		
Injection, for IM use only	50 mg (of haloperidol) per mL*	Haldol® Decanoate, Ortho-McNeil (also promoted by Scios Nova)
		Haloperidol Decanoate Injection
	100 mg (of haloperidol) per mL*	Haldol® Decanoate, Ortho-McNeil (also promoted by Scios Nova)
		Haloperidol Decanoate Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

Haloperidol Lactate

Oral		
Solution	2 mg (of haloperidol) per mL*	Haloperidol Lactate Oral Solution Concentrate
Parenteral		
Injection	5 mg (of haloperidol) per mL*	Haldol®, Ortho-McNeil
		Haloperidol Lactate Injection

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

†Use is not currently included in the labeling approved by the US Food and Drug Administration

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PHENOTHIAZINES 28:16.08.24

Phenothiazines General Statement

■ Phenothiazines are conventional (prototypical, first-generation) antipsychotic agents.

Uses

Phenothiazines mainly are used for the management of various psychoneurologic disorders and for the prevention and control of nausea and vomiting. The efficacy of individual phenothiazines varies in different neuropsychiatric and other conditions, and some phenothiazines are not used as antipsychotic agents. Promethazine is used as an antihistamine (see 4:04) and as a sedative (see 28:24.92) and thiethylperazine as an antiemetic. For further information, see the individual monographs on these derivatives.

■ **Psychotic Disorders** ***Schizophrenia and Other Psychotic Disorders*** Phenothiazines are used principally for the symptomatic management of psychotic disorders, especially those characterized by excessive psychomotor activity. The drugs produce substantial improvement in most schizophrenic patients. Phenothiazines are particularly effective in reducing hallucinations and motor and autonomic hyperactivity in patients with schizophrenic disorder; thought disorders, change in affect, and autism are also reduced during phenothiazine therapy. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

General Considerations. Schizophrenia, a major psychotic disorder, is a chronic condition that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of the disorder involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The behavioral and psychologic characteristics of schizophrenia are associated with a variety of impairments in social and occupational functioning. Although marked deterioration associated with impairments in multiple areas of functioning (e.g., learning, self-care, working, interpersonal relationships, living skills) can occur, the disorder is characterized by great interindividual heterogeneity and by intraindividual variability over time.

The principal manifestations of schizophrenia usually are described in terms of positive and negative (deficit) symptoms and, more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. Subtypes of schizophrenia include the paranoid, disorganized, catatonic, undifferentiated, and residual types.

Management of schizophrenia usually involves a variety of interventions (e.g., psychiatric management, psychosocial interventions, drug therapy, electroconvulsive therapy [ECT]) aimed at reducing or eliminating symptoms, maximizing quality of life and adaptive functioning, and enabling recovery by assisting patients in attaining personal life goals (e.g., in work, housing, relationships). The long-term outcome of schizophrenia varies along a continuum between reasonable recovery and complete incapacity. Most patients display exacerbations and remissions in the context of experiencing clinical deterioration, although approximately 10–15% of patients are free of further episodes after recovery from a first psychotic episode, and another 10–15% remain chronically severely psychotic.

Disease Phase Overview. Schizophrenia is a disorder that has been described as developing in phases, which have been characterized as premorbid, prodromal, and psychotic. The premorbid phase consists of a period of normal functioning, although certain events (e.g., complications in pregnancy and delivery during the prenatal and perinatal periods, trauma, family stress during

Olanzapine for IM injection should not be combined with diazepam injection in a syringe because precipitation occurs when these drugs are mixed. Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting pH has been shown to degrade olanzapine over time. Specialized references should be consulted for additional specific compatibility information.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Olanzapine

Oral		
Tablets, film-coated	2.5 mg	Zyprexa®, Lilly
	5 mg	Zyprexa®, Lilly
	7.5 mg	Zyprexa®, Lilly
	10 mg	Zyprexa®, Lilly
	15 mg	Zyprexa®, Lilly
	20 mg	Zyprexa®, Lilly
Tablets, orally disintegrating	5 mg	Zyprexa® Zydis®, Lilly
	10 mg	Zyprexa® Zydis®, Lilly
	15 mg	Zyprexa® Zydis®, Lilly
	20 mg	Zyprexa® Zydis®, Lilly
Parenteral		
For injection	10 mg	Zyprexa® IntraMuscular, Lilly

Olanzapine Combinations

Oral		
Capsules	6 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	Symbyax®, Lilly
	6 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	Symbyax®, Lilly
	12 mg with Fluoxetine Hydrochloride 25 mg (of fluoxetine)	Symbyax®, Lilly
	12 mg with Fluoxetine Hydrochloride 50 mg (of fluoxetine)	Symbyax®, Lilly

†Use is not currently included in the labeling approved by the US Food and Drug Administration

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Paliperidone

9-Hydroxyrisperidone

■ Paliperidone is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Paliperidone is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Paliperidone is used orally for the acute and maintenance treatment of schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

The short-term efficacy of paliperidone in the acute treatment of schizophrenia was established in 3 placebo-controlled and active comparator (olanzapine)-controlled, fixed-dose clinical trials of 6 weeks' duration in 1665 adult patients with schizophrenia. In these 3 studies, patients receiving paliperidone (3–15 mg daily as extended-release tablets) demonstrated substantially greater improvement in the Positive and Negative Syndrome Scale (PANSS) than did patients receiving placebo. The mean effects at all dosages (3, 6, 9, 12, and 15 mg daily) were fairly similar, although higher dosages produced numerically superior results. Paliperidone also was found to be superior to placebo in improving scores on the Personal and Social Performance (PSP) scale in these trials.

In a longer-term study, adult outpatients with schizophrenia who had clinically responded to oral paliperidone and who had received a stable fixed dosage of the drug for 2 weeks entered a 6-week, open-label, stabilization phase where they received a paliperidone dosage from 3–15 mg once daily as extended-release tablets. After the stabilization phase, patients were randomized in a double-blind manner to either continue receiving paliperidone at their stable dosage or to receive placebo until they experienced a relapse of schizophrenia symptoms. The median treatment exposure during this double-blind phase was 45 days for extended-release paliperidone and 29 days for placebo; the mean paliperidone dosage was approximately 11 mg daily throughout the phases of this trial. An interim analysis of the data showed a significantly longer time to relapse in the paliperidone-treated patients compared with those receiving placebo. In addition, 52% of the paliperidone-treated patients experienced a relapse compared with 22% of those receiving placebo. The study was stopped early because maintenance of efficacy was demonstrated. If paliperidone is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

The American Psychiatric Association (APA) considers most atypical antipsychotic agents first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

Dosage and Administration

■ **Administration** Paliperidone is administered orally once daily in the morning with or without food.

Paliperidone extended-release tablets should be swallowed whole with fluids and should *not* be chewed, divided, or crushed. Patients should be advised *not* to become concerned if they notice a tablet-like substance in their stools; this is normal since the tablet is designed to remain intact and slowly release the drug from a nonabsorbable shell during passage through the GI tract.

■ **Dosage** ***Schizophrenia*** For the management of schizophrenia, the usual recommended dosage of paliperidone in adults is 6 mg once daily in the morning; dosage titration is not required. Although it remains to be systematically evaluated whether dosages exceeding 6 mg once daily provide additional clinical benefit, a general trend for greater clinical effects with higher dosages has been observed. However, the potential for increased clinical efficacy at higher dosages must be weighed against the potential for a dose-related increase in adverse effects. Some patients may benefit from higher dosages of up to 12 mg once daily, while a lower dosage of 3 mg once daily may be sufficient for other patients. The manufacturer states that increases beyond a dosage level of 6 mg once daily should be made only after clinical reassessment and generally should be made at intervals of more than 5 days. When dosage increases are necessary, increments of 3 mg daily are recommended. The maximum recommended dosage is 12 mg once daily.

The optimum duration of oral paliperidone therapy in patients with schizophrenia currently is not known, but maintenance therapy with paliperidone 3–15 mg daily as extended-release tablets has been shown to be effective in preventing relapse. Patients responding to paliperidone therapy should continue to receive the drug as long as clinically necessary and tolerated but at the lowest possible effective dosage, and the need for continued therapy with the drug should be reassessed periodically. The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with schizo-

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phrenia with remitted first- or multiple-episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

■ **Special Populations** Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). (See Hepatic Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

In patients with renal impairment, the maximum recommended dosage of paliperidone is 6 mg once daily in those with mild renal impairment (creatinine clearance of 50–79 mL/minute) and 3 mg once daily in those with moderate to severe renal impairment (creatinine clearance of 10–49 mL/minute). (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

Because geriatric patients may have reduced renal function, dosage adjustment may be required based on renal function status. Geriatric patients with normal renal function generally may receive the same dosage recommended for younger adults with normal renal function. In geriatric patients with moderate to severe renal impairment, the maximum recommended paliperidone dosage is 3 mg once daily. (See Renal Impairment under Warnings/Precautions: Specific Populations, in Cautions.)

No dosage adjustment is necessary based on gender or race.

Cautions

■ **Contraindications** Known hypersensitivity to paliperidone, risperidone, or any ingredient in the formulation.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Analysis of 17 placebo-controlled trials (average duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that in patients receiving placebo. Over the course of a typical 10-week controlled study, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. In addition, an increased incidence of cerebrovascular adverse effects (e.g., stroke, transient ischemic attack), including fatalities, has been observed in geriatric patients treated with aripiprazole, olanzapine, and risperidone in placebo-controlled studies of dementia-related psychosis. The manufacturer states that paliperidone is not approved for the treatment of patients with dementia-related psychosis. (See Dosage and Administration: Special Populations and see also Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Prolongation of QT Interval. Paliperidone causes a modest increase in the corrected QT (QT_c) interval. The risk of torsades de pointes in association with drugs that prolong the QT_c interval may be increased in patients with bradycardia, hypokalemia, or hypomagnesemia; patients receiving other drugs that prolong the QT_c interval; and in those with congenital prolongation of the QT interval. Therefore, the manufacturer states that paliperidone should be avoided in patients concurrently receiving other drugs known to prolong the QT_c interval, patients with congenital long QT syndrome, and those with a history of cardiac arrhythmias. (See Drugs that Prolong QT Interval under Drug Interactions.)

Neuroleptic Malignant Syndrome. Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including paliperidone. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Because use of antipsychotic agents may be associated with tardive dyskinesia, a syndrome of potentially irreversible, involuntary, dyskinetic movements, paliperidone should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The American Psychiatric Association (APA) currently recommends that patients receiving second-generation antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with all atypical antipsychotic agents. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotic agents. Because paliperidone was not marketed at the time these studies were performed, it is unknown if the drug is associated with this increased risk; however, there have been 2 cases of hyperglycemia or diabetes reported to date in paliperidone-treated patients in clinical trials.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (e.g., polydipsia, polyphagia, polyuria, weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Cautions: Endocrine and Metabolic Effects and see also Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

GI Effects. As with other nondeformable material, extended-release paliperidone tablets do not appreciably change in shape in the GI tract. Therefore, the drug generally should not be administered to patients with severe, preexisting GI narrowing (either pathological or iatrogenic). Rare cases of obstructive symptoms in patients with known strictures have been reported in association with the ingestion of drugs in nondeformable, controlled-release formulations. Because of the extended-release design of paliperidone tablets, the drug should only be used in patients who are able to swallow the tablet whole.

Decreased bioavailability of paliperidone extended-release tablets would be expected in patients with a decreased GI transit time (e.g., those with diarrhea) while an increased bioavailability would be expected in patients with an increased GI transit time (e.g., those with GI neuropathy, diabetic gastroparesis, or due to other causes). Such changes in bioavailability are more likely when changes in transit time occur in the upper GI tract.

General Precautions **Orthostatic Hypotension and Syncope.** Orthostatic hypotension and syncope have been reported. Syncope occurred in about 0.8% of patients receiving paliperidone in controlled clinical trials. Use with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities) or cerebrovascular disease and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy). Consider monitoring of orthostatic vital signs in patients who may be vulnerable to hypotension (e.g., geriatric patients).

Seizures. Seizures have occurred in approximately 0.2% of patients receiving paliperidone in controlled clinical studies. Use with caution in patients with a history of seizures or other conditions that may lower the seizure threshold (e.g., dementia of the Alzheimer's type, geriatric patients).

Hyperprolactinemia. Similar to other antipsychotic agents, paliperidone causes elevated prolactin concentrations, which may persist during chronic administration. Paliperidone's prolactin-elevating effects are similar to those seen with risperidone, which appears to be associated with a higher level of prolactin elevation than other currently available antipsychotic agents. Clinical disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been associated with prolactin-elevating drugs. In addition, chronic hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in males and females. However, the clinical importance of elevated prolactin concentrations is unknown for most patients.

Dysphagia. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents. Use with caution in patients at risk for aspiration pneumonia (e.g., patients with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Suicide. Attendant risk with psychotic illnesses; closely supervise high-risk patients. Prescribe in the smallest quantity consistent with good patient management to reduce the risk of overdosage.

Somnolence. Somnolence and sedation have been reported in patients receiving paliperidone therapy.

Sexual Dysfunction. Although priapism has not been reported in clinical trials of paliperidone, the drug possesses α-adrenergic blocking activity and may therefore be associated with this risk.

Hematologic Effects. Thrombotic thrombocytopenic purpura (TTP) has not been reported in clinical trials of paliperidone. TTP has been reported in association with risperidone therapy; however, the relationship of this adverse event to risperidone is unknown.

Body Temperature Regulation. Disruption of the body's ability to reduce core body temperature has been associated with the use of antipsychotic agents. Use caution when paliperidone is administered in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

Antiemetic Effects. Antiemetic effects were observed in preclinical studies with paliperidone; these effects also may occur in humans and mask signs of overdosage of other drugs or obscure cause of vomiting in various disorders (e.g., intestinal obstruction, Reye's syndrome, brain tumor).

Patients with Concomitant Illness. Clinical experience with paliperidone in patients with certain concomitant illnesses is limited.

Patients with parkinsonian syndrome or dementia with Lewy bodies who receive antipsychotics, including paliperidone, reportedly have an increased sensitivity to antipsychotic agents. Clinical manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and features consistent with NMS. (For additional information on extrapyramidal adverse effects and NMS, see Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.)

Paliperidone has not been adequately evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease to date and patients with these conditions were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension associated with paliperidone, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease. (See Orthostatic Hypotension and Syncope under Warnings/Precautions/General Precautions, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Paliperidone is distributed into milk in animals. Both risperidone and 9-hydroxyrisperidone, which is the major active metabolite of risperidone and the same drug as paliperidone, distribute into milk following risperidone administration in humans. The manufacturer states that women receiving paliperidone should not breast-feed.

Pediatric Use. Safety and effectiveness not established in pediatric patients younger than 18 years of age.

Geriatric Use. In clinical studies, approximately 7% of nearly 1800 patients were 65 years of age or older. In addition, the short-term efficacy and safety of paliperidone have been demonstrated in a placebo-controlled trial of 6 weeks' duration in 114 geriatric patients with schizophrenia. While no substantial differences in efficacy or safety relative to younger adults were observed in these studies or in other clinical experience with the drug, increased sensitivity cannot be ruled out.

Because geriatric patients may have reduced renal function, dosage adjustment may be required based on renal function status; consider monitoring renal function. (See Dosage and Administration: Special Populations.)

Geriatric patients with dementia-related psychosis treated with atypical antipsychotic drugs appear to be at an increased risk of death compared with that among patients receiving placebo. Paliperidone is *not* approved for the treatment of dementia-related psychosis. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Hepatic Impairment. Patients with moderate hepatic impairment (Child-Pugh class B) exhibited similar plasma concentrations of free paliperidone as healthy individuals, although total paliperidone exposure decreased because of decreased protein binding. Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). The effect of severe hepatic impairment on paliperidone pharmacokinetics is not known. (See Dosage and Administration: Special Populations.)

Renal Impairment. Clearance decreased by an average of 32, 64, and 71% in patients with mild, moderate, and severe renal impairment, respectively. Dosage adjustment is recommended in patients with moderate or severe renal impairment. (See Dosage and Administration: Special Populations.)

■ **Common Adverse Effects** Adverse effects reported in 5% or more of patients receiving paliperidone include tremor, headache, orthostatic hypotension, tachycardia, somnolence, akathisia, insomnia, anxiety, extrapyramidal reaction, dizziness, dystonia, QT_c interval prolongation, nausea, dyspepsia, and weight gain.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Inhibitors or inducers of cytochrome P-450 (CYP) isoenzymes 2D6, 3A4, 1A2, 2A6, 2C9, and 2C19: pharmacokinetic interaction unlikely.

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, or CYP3A5: pharmacokinetic interaction unlikely.

■ **Drugs Inhibiting P-glycoprotein Transport System** At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein; clinically relevant interactions unlikely.

■ **Drugs that Prolong QT Interval** Potential pharmacologic interaction (additive effect on QT-interval prolongation); avoid concomitant use of other drugs known to prolong the QT interval (e.g., amiodarone, quinidine, procainamide, sotalol; other Class Ia and III antiarrhythmics, chlorpromazine, thioridazine, gatifloxacin, moxifloxacin).

■ **Protein-bound Drugs** Pharmacokinetic interaction unlikely.

■ **Alcohol** Potential pharmacologic interaction (additive sedative effects). Avoid alcoholic beverages during paliperidone therapy.

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects).

■ **Levodopa and Dopamine Agonists** Potential pharmacologic interaction (antagonistic effects).

■ **Paroxetine** Concomitant administration of paroxetine (20 mg daily) and a single dose of paliperidone (3 mg as extended-release tablets) caused a small, clinically insignificant increase in paliperidone area under the concentration-time curves (AUCs) compared with paliperidone administration alone. Therefore, dosage adjustment of paliperidone is not neeessary.

■ **Risperidone** Concurrent use of paliperidone with risperidone has not been studied to date. However, because paliperidone is the prineipal active metabolite of risperidone, consideration should be given to additive paliperidone exposure if risperidone and paliperidone are coneomitantly administered.

■ **Other CNS Agents** Potential pharmacologic interaction (additive sedative effeets). Use with caution.

■ **Smoking** Pharmacokinetic interaction unlikely. Dosage adjustment in patients who smoke is not necessary.

Description

Paliperidone is a benzisoxazole-derivative antipsyehotic agent that differs chemieally from other currently available first-generation (typical) antipsychotic agents (e.g., butyrophenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotie agent. The drug is the major active metabolite of risperidone, another atypical antipsychotic agent.

The exact mechanism of paliperidone's antipsychotic action, like that of other antipsychotic agents, has not been fully elucidated, but may involve antagonism of central dopamine type 2 (D_2) and serotonin type 2 (5-hydroxytryptamine [$5\text{-}HT_{2A}$]) receptors. Antagonism at α_1- and α_2-adrenergic and histamine (H_1) receptors may contribute to other therapeutic and adverse effects observed with the drug. Paliperidone possesses no affinity for eholinergic muscarinic and β_1- and β_2-adrenergic receptors.

In vitro studies have suggested a role for cytochrome P-450 (CYP) isoenzymes 2D6 and 3A4 in the metaholism of paliperidone; however, the results of in vivo studies indicate that these isoenzymes play a limited role in the overall elimination of the drug from the body.

Approximately 80% and 11% of a single 1-mg oral dose of radiolabeled, immediate-release paliperidone is recovered in urine and feces, respectively, within 1 week. About 59% of the administered dose is recovered as unchanged drug and 32% recovered as metabolites. Following single-dose oral administration as extended-release tablets, paliperidone appears to have a mean terminal elimination half-life of about 23 hours.

Advice to Patients

Importance of reading manufacturer's patient information.

Risk of orthostatic hypotension, particularly during initial dosage titration and at times of reinitiation of therapy or increases in dosage. Importance of advising patients who experience dizziness or fainting during therapy to get up slowly when sitting or lying down.

Because somnolenee and impairment of judgment, thinking, or motor skills may be associated with paliperidone, patients should be cautioned about driving, operating machinery, or performing hazardous tasks while taking paliperidone until they gain experience with the drug's effects. Importance of avoiding alcohol during paliperidone therapy.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription (see Drug Interactions: Drugs that Prolong QT Interval) and OTC drugs, dietary supplements, and/or herbal products, as well as any concomitant illnesses (e.g., cardiovascular disease, diabetes mellitus, seizures).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

Importance of informing patients that paliperidone tablets should be swallowed whole with the aid of liquids, and should not be chewed, divided or crushed. Patients should not be concerned if they notice a tablet-like substance in their stool.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview[a] (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufac-

turer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Paliperidone

Oral

Tablets, extended-release	3 mg	Invega®, Janssen
	6 mg	Invega®, Janssen
	9 mg	Invega®, Janssen

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Quetiapine Fumarate

■ Quetiapine is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Quetiapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Short-term efficacy of quetiapine for the management of schizophrenia has been established by placebo-controlled studies of 6 weeks' duration principally in hospitalized patients with schizophrenia. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms, and more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

In clinical studies in patients with schizophrenia, quetiapine was more effective than placebo in reducing the severity of symptoms associated with this disorder. Quetiapine appears to improve both positive and negative manifestations of schizophrenia. Results from comparative clinical studies and meta-analyses suggest that quetiapine is at least as effective as chlorpromazine or haloperidol in reducing positive and negative symptoms of schizophrenia.

The American Psychiatric Association (APA) considers certain atypical antipsychotic agents (i.e., quetiapine, aripiprazole, olanzapine, risperidone, ziprasidone) first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

Although the efficacy of quetiapine for long-term use has not been established in controlled studies, the manufacturer states that beneficial effects of the drug were maintained for up to 4 years in some patients during an open-label extension study in patients who achieved an initial response to treatment during double-blind clinical studies. If quetiapine is used for extended periods, the need for continued therapy should be reassessed periodically on an individualized basis. (See Dosage and Administration: Dosage.)

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Quetiapine is used alone or in conjunction with lithium or divalproex sodium for the management of acute manic episodes associated with bipolar I disorder. Efficacy of quetiapine monotherapy in the treatment of acute manic episodes has been demonstrated in 2 placebo-controlled studies of 12 weeks' duration in patients who met the DSM-IV criteria for bipolar disorder and who met diagnostic criteria for an acute manic episode (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from these studies. The principal rating instrument used for assessing manic symptoms in these studies was the Young Mania Rating Scale (YMRS) score, an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). In these studies, quetiapine was shown to be superior to placebo in reduction of the YMRS total score after 3 and 12 weeks of treatment.

Efficacy of quetiapine when used in combination with lithium or divalproex sodium in the management of acute manic episodes has been demonstrated in a placebo-controlled study of 3 weeks' duration in patients who met the DSM-IV criteria for bipolar I disorder with acute manic episodes (with or without psychotic features). Patients with rapid cycling and mixed episodes were excluded from enrollment and patients included in the study may or may not have received an adequate course of therapy with lithium or divalproex sodium prior to randomization. Quetiapine was shown to be superior to placebo when added to lithium or divalproex sodium alone in the reduction of YMRS total score. However, in a similarly designed study, quetiapine was associated with an improvement of YMRS scores but did not demonstrate superiority to placebo.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic (e.g., olanzapine) may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

Quetiapine also is used for the treatment of depressive episodes associated with bipolar disorder. Efficacy of quetiapine in the treatment of depressive episodes has been demonstrated in 2 randomized, double-blind, placebo-controlled studies of 8 weeks' duration in patients with bipolar I or II disorder (with or without a rapid cycling course). Patients in these studies received fixed daily quetiapine dosages of 300 or 600 mg once daily. The principal rating instrument used for assessing depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. In both studies, quetiapine was found to be superior to placebo in reduction of MADRS scores at week 8, with improvements in scores evident within one week of treatment. In addition, patients receiving 300 mg of quetiapine daily demonstrated significant improvements compared to placebo recipients in overall quality of life and satisfaction related to various areas of functioning.

Dosage and Administration

■ **Administration** Quetiapine is administered orally. While food reportedly can marginally increase the peak concentration and oral bioavailability of quetiapine, the drug generally can be administered without regard to meals.

Dispensing and Administration Precautions Because of similarity in spelling between Seroquel® (the trade name for quetiapine fumarate) and Serzone® (the former trade name for nefazodone hydrochloride, an antidepressant agent; no longer commercially available in the US under this trade name), dispensing errors have been reported to the US Food and Drug Administration (FDA) and the manufacturer of Seroquel® (AstraZeneca). According to the medication error reports, the overlapping strengths (100 and 200 mg), dosage forms (tablets), and dosing intervals (twice daily) and the fact that these 2 drugs were stored closely together in pharmacies also were critical in causing these errors. Therefore, extra care should be exercised in ensuring the accuracy of both oral and written prescriptions for Seroquel® and Serzone®. Although the Serzone brand was discontinued in June 2004, clinicians may continue to refer to nefazodone by the former brand name in prescribing. Some experts recommend that pharmacists assess the measures of avoiding dispensing errors and implement them as appropriate (e.g., by verifying all orders for these agents by spelling both the trade and generic names to prescribers, using computerized name alerts, attaching reminders to drug containers and pharmacy shelves, separating the drugs on pharmacy shelves, counseling patients). (See Dispensing and Administration Precautions under Warnings/Precautions: General Precautions in Cautions.)

■ **Dosage** Dosage of quetiapine fumarate is expressed in terms of quetiapine and must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage.