

WARNINGS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. HALDOL Injection is not approved for the treatment of patients with dementia-related psychosis (see [BOXED WARNING](#)).

Cardiovascular Effects

Cases of sudden death, QT-prolongation, and Torsades de Pointes have been reported in patients receiving HALDOL. Higher than recommended doses of any formulation and intravenous administration of HALDOL appear to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, [hypothyroidism](#), and [familial](#) long QT-syndrome). **HALDOL INJECTION IS NOT APPROVED FOR INTRAVENOUS ADMINISTRATION.** If HALDOL is administered intravenously, the ECG should be monitored for QT prolongation and arrhythmias.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase.

However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the

syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a [chronic illness](#) that, 1) is known to respond to antipsychotic drugs, and, 2) 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. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to [ADVERSE REACTIONS](#).)

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or [blood pressure](#), [tachycardia](#), diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria ([rhabdomyolysis](#)) and [acute renal failure](#).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., [pneumonia](#), systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the [differential diagnosis](#) include central anticholinergic toxicity, [heat stroke](#), drug fever and primary [central nervous system \(CNS\) pathology](#).

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with HALDOL.

Usage in Pregnancy

Rodents given 2 to 20 times the usual maximum human dose of haloperidol by oral or parenteral routes showed an increase in incidence of resorption, reduced [fertility](#), delayed delivery and pup mortality. No teratogenic effect has been reported in rats, rabbits or dogs at dosages within this range, but [cleft palate](#) has been observed in mice given 15 times the usual maximum human dose. Cleft palate in mice appears to be a nonspecific response to [stress](#) or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no well controlled studies with HALDOL (haloperidol) in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of HALDOL along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to HALDOL, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the [fetus](#). Infants should not be nursed during drug treatment.

Combined Use of HALDOL and Lithium

An [encephalopathic syndrome](#) (characterized by weakness, [lethargy](#), fever, tremulousness and confusion, extrapyramidal symptoms, [leukocytosis](#), elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus HALDOL. A causal relationship between these events and the concomitant administration of lithium and HALDOL has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

General

A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including HALDOL. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to [dehydration](#), hemoconcentration and reduced pulmonary

ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with HALDOL, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

HALDOL may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

SIDE EFFECTS

Cardiovascular Effects

[Tachycardia](#), [hypotension](#), and [hypertension](#) have been reported. QT prolongation and/or [ventricular arrhythmias](#) have also been reported, in addition to ECG pattern changes compatible with the polymorphous configuration of torsade de pointes, and may occur more frequently with high doses and in predisposed patients (see [WARNINGS](#) and [PRECAUTIONS](#)).

Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The [nature](#) of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other [antipsychotic](#) drugs.

CNS Effects

Extrapyramidal Symptoms (EPS)

EPS during the administration of HALDOL (haloperidol) have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, [akathisia](#), or [dystonia](#) (including [opisthotonos](#) and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson

drugs such as benztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the [tongue](#). While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of HALDOL.

Tardive Dyskinesia

As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive [dyskinesia](#), a syndrome consisting of potentially irreversible, [involuntary](#), dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or [jaw](#) (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia

Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects

[Insomnia](#), restlessness, [anxiety](#), [euphoria](#), agitation, drowsiness, [depression](#), [lethargy](#), [headache](#), confusion, [vertigo](#), grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole

Neuroleptic malignant syndrome (NMS), hyperpyrexia and [heat stroke](#) have been reported with HALDOL. (See [WARNINGS](#) for further information concerning NMS.)

Hematologic Effects

Reports have appeared citing the occurrence of mild and usually transient [leukopenia](#) and [leukocytosis](#), minimal decreases in [red blood cell](#) counts, [anemia](#), or a tendency toward lymphomonocytosis. [Agranulocytosis](#) has rarely been reported to have occurred with the use of HALDOL, and then only in association with other medication.

Liver Effects

Impaired liver function and/or [jaundice](#) have been reported.

Dermatologic Reactions

Maculopapular and acneiform skin reactions and isolated cases of [photosensitivity](#) and loss of hair.

Endocrine Disorders

[Lactation](#), breast engorgement, [mastalgia](#), menstrual irregularities, [gynecomastia](#), [impotence](#), increased [libido](#), [hyperglycemia](#), [hypoglycemia](#) and [hyponatremia](#).

Gastrointestinal Effects

[Anorexia](#), [constipation](#), [diarrhea](#), hypersalivation, [dyspepsia](#), [nausea](#) and vomiting.

Autonomic Reactions

[Dry mouth](#), [blurred vision](#), urinary retention, diaphoresis and [priapism](#).

Respiratory Effects

Laryngospasm, bronchospasm and increased depth of [respiration](#).

Special Senses

Cataracts, retinopathy and visual disturbances.

Postmarketing Events

Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of [ammonia](#) excretion, following treatment with HALDOL.