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USE OF HALOPERIDOL IN PSYCHIATRY

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ABSTRACT

Haloperidol, marketed under the trade name Haldol among others, is a typical antipsychotic medication. Indications Acute and chronic psychotic disorders including: schizophrenia, manic states, druginduced psychoses. Patients with schizophrenia who require long-term parenteral (IM) antipsychotic therapy. Also useful in managing aggressive or agitated patients. Tourette's syndrome. Action Alters the effects of dopamine in the CNS. Also has anticholinergic and alpha-adrenergic blocking activity. Contraindications/Precautions Contraindicated in: Hypersensitivity; Angle-closure glaucoma; Bone marrow depression; CNS depression; Parkinsonism.Adverse Reactions/Side Effects CNS, SEIZURES, extrapyramidal reactions, confusion, drowsiness, restlessness, tardive dyskinesia. EENT: blurred vision, dry eyes. Resp: respiratory depression. For maintenance treatment of schizophrenia, an international consensus conference recommended a reduction dosage by about 20% every 6 months until a minimal maintenance dose is established. Topical formulations of haloperidol should not be used as treatment for nausea because research does not indicate this therapy is more effective than alternatives.

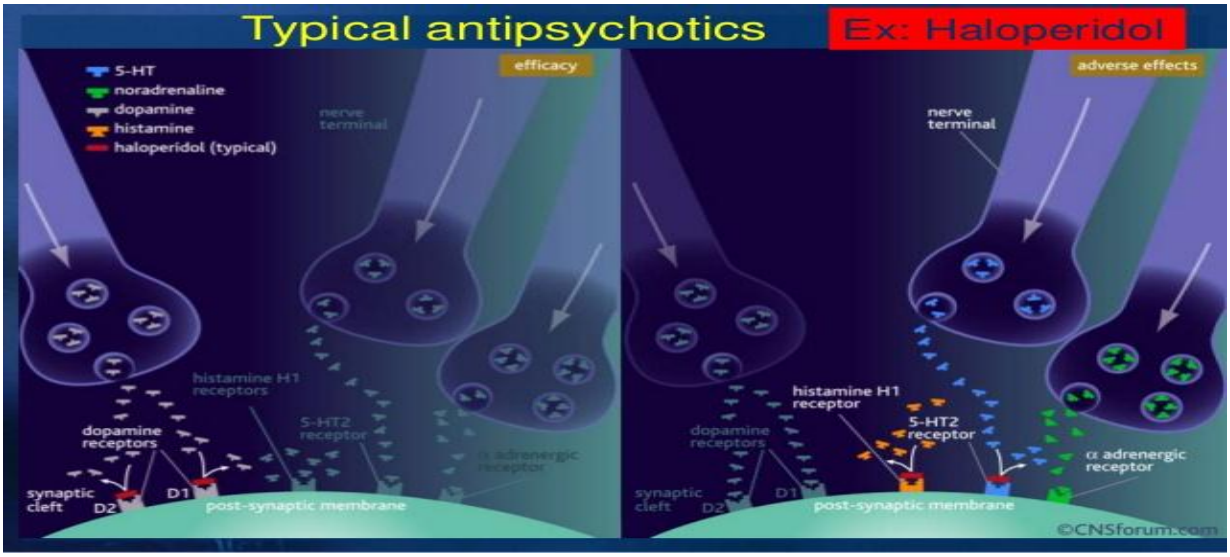
KEYWORDS: Parkinson'sdisease; Psychosis; Hallucinations; Delusions; Atypicalanti-psychoticdrugs; Dementia.

INTRODUCTION AND HISTORY

Haloperidol, marketed under the trade name **Haldol** among others, is a typical antipsychotic medication.[1][2][3] Haloperidol is used in the treatment of schizophrenia, tics in Tourette syndrome, mania in bipolar disorder, nausea and vomiting, delirium, agitation, acutepsychosis, and hallucinations in alcohol withdrawal.[3][4][5] It may be used by mouth, as an injection into a muscle, or intravenously. Haloperidol typically works within thirty to sixty minutes. A long-acting formulation may be used as an injection every four weeks in people with schizophrenia or related illnesses, who either forget or refuse to take the medication by mouth.[3]Haloperidol may result in a movement disorder known as tardive dyskinesia which may be permanent. Neuroleptic malignant syndrome and QT interval prolongation may occur. In older people with psychosis due to dementia it results in an increased risk of death.[3] When taken during pregnancy it may result in problems in the infant.[3][6] It should not be used in people with Parkinson's disease.[3]Haloperidol was discovered in 1958 by Paul Janssen.[7] It was made from meperidine.[8] It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system.[9] It is the most commonly used typical antipsychotic.[10] The yearly cost of the typical dose of haloperidol is about 20 to 800 pounds (30 to 1,250 US dollars) in the United Kingdom.[10][11] The cost in the United States is around 250 US dollars a year.[12]

Indications Acute and chronic psychotic disorders including: schizophrenia, manic states, druginduced psychoses. Patients with schizophrenia who require long-term parenteral (IM) antipsychotic therapy. Also useful in managing aggressive or agitated patients. Tourette's syndrome. Severe behavioral problems in children which may be accompanied by: unprovoked, combative, explosive hyperexcitability, hyperactivity accompanied by conduct disorders (short-term use when other modalities have failed). Considered second-line treatment after failure with atypical antipsychotic.[13] Unlabeled Use: Nausea and vomiting from surgery or chemotherapy.

Action Alters the effects of dopamine in the CNS. Also has anticholinergic and alpha-adrenergic blocking activity.[14,15,16] Therapeutic Effects: Diminished signs and symptoms of psychoses. Improved behavior in children with Tourette's syndrome or other behavioral problems.



Pharmacokinetics

Absorption[17,18,19,20]: Well absorbed following PO/IM administration. Decanoate salt is slowly absorbed and has a long duration of action.

Distribution: Concentrates in liver. Crosses placenta; enters breast milk. Protein Binding: 92%.

Metabolism and Excretion: Mostly metabolized by the liver. Half-life: 21– 24 hr. TIME/ACTION PROFILE (antipsychotic activity) ROUTE ONSET PEAK DURATION PO 2 hr 2–6 hr 8–12 hr IM 20–30 min 30–45 min 4–8 hr† IM (decanoate) 3–9 days unknown 1 mo †Effect may persist for several days.

Contraindications/Precautions Contraindicated in

Hypersensitivity; Angle-closure glaucoma; Bone marrow depression; CNS depression; Parkinsonism; Severe liver or cardiovascular disease (QT interval prolonging conditions); Some products contain tartrazine, sesame oil, or benzyl alcohol and should be avoided in patients with known intolerance or hypersensitivity.[21,21] Use Cautiously in: Debilitated patients (doseprequired); Cardiac disease (risk of QT prolongation with high doses); Diabetes; Respiratory insufficiency; Prostatic hyperplasia; CNS tumors; Intestinal obstruction; Seizures; OB: Neonates atqrisk for extrapyramidal symptoms and withdrawal after delivery when exposed during the 3rd trimester; use only if benefit outweighs risk to fetus; Lactation: Discontinue drug or bottle-feed; Geri: Doseprequired due toqsensitivity;qrisk of mortality in elderly patients treated for dementia-related psychosis.

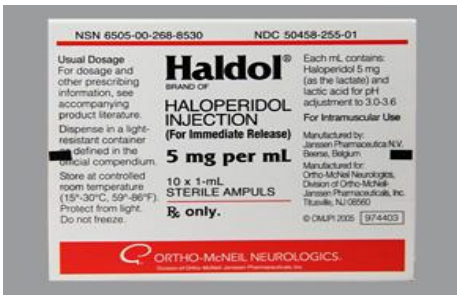
Adverse Reactions/Side Effects CNS.[23,24,25,26]

SEIZURES, extrapyramidal reactions, confusion, drowsiness, restlessness, tardive dyskinesia. EENT: blurred vision, dry eyes. Resp: respiratory depression. CV: hypotension, tachycardia, ECG changes (QT prolongation, torsade de pointes), ventricular arrhythmias. GI: constipation, dry mouth, anorexia, drug-induced hepatitis, ileus, weight gain.GU: impotence, urinary retention. Derm: diaphoresis, photosensitivity, rashes. Endo: amenorrhea, galactorrhea, gynecomastia. Hemat: AGRANULOCYTOSIS, anemia, leukopenia, neutropenia. Metab: hyperpyrexia. Misc: NEUROLEPTIC MALIGNANT SYNDROME, hypersensitivity reactions. Interactions Drug-Drug: May enhance the QTc-prolonging effect of QTc-prolonging agents. qhypotension with antihypertensives, nitrates, or acute ingestion of alcohol.q anticholinergic effects with drugs having anticholinergic properties, including antihistamines, antidepressants, atropine, phenothiazines, quinidine, and disopyramide. qCNS depression with other CNS depressants, including alcohol, antihistamines, opioid analgesics, and sedative/hypnotics. Concurrent use with epinephrine may result in severe hypotension and tachycardia. Maytherapeutic effects of levodopa. Acute encephalopathic syndrome may occur when used with lithium. Dementia may occur with methyldopa. Drug-Natural Products: Kava-kava, valerian, or chamomile canq CNS depression.

Route/Dosage Haloperidol PO (Adults).[27,28,29,30]

0.5– 5 mg 2– 3 times daily. Patients with severe symptoms may require up to 100 mg/day. PO (Geriatric Patients or Debilitated Patients): 0.5– 2 mg twice daily initially; may be graduallyqas needed. PO (Children 3–12 yr or 15– 40 kg): 0.25– 0.5 mg/day given in 2– 3 divided doses; increase by 0.25– 0.5 mg every 5– 7 days; maximum dose: 0.15 mg/kg/day (up to 0.75 mg/kg/day for Tourette's syndrome or 0.15 mg/kg/day for psychoses). IM (Adults): 2– 5 mg q 1– 8 hr (not to exceed 100 mg/day). IM (Children 6– 12 yr): 1– 3 mg/dose every 4– 8 hours to a maximum of 0.15 mg/kg/day. IV (Adults): 0.5– 5 mg, may be repeated q 30 min (unlabeled).

Haloperidol Decanoate IM (Adults): 10– 15 times the previous daily PO dose but not to exceed 100 mg initially, given monthly (not to exceed 300 mg/mo).

BRAND	FORM.	PILL IMAGE
Haldol	5mg/mLsolution	
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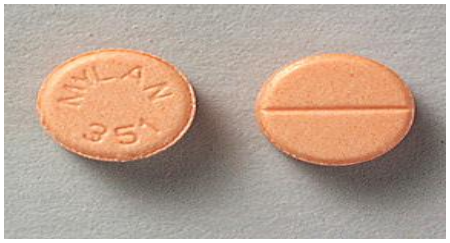
haloperidol	20mgtablet	
haloperidol	5mgtablet	
haloperidol	0.5mgtablet	
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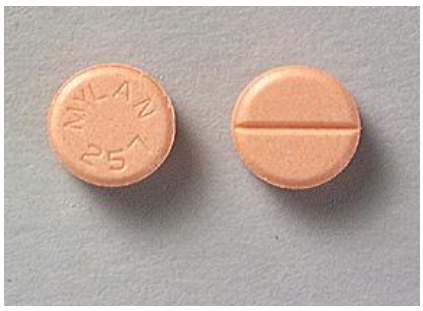
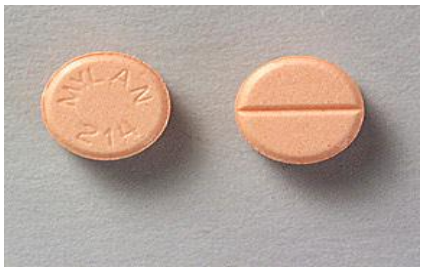
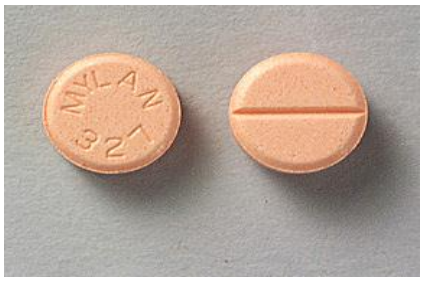
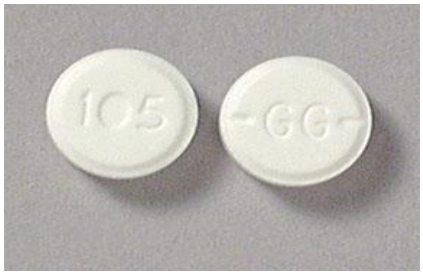
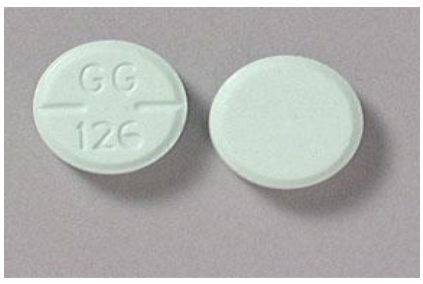
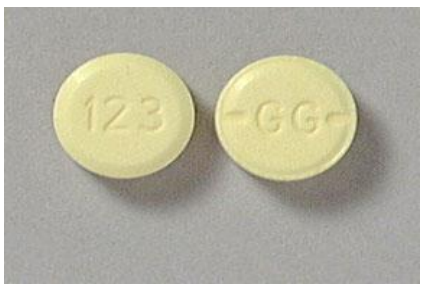
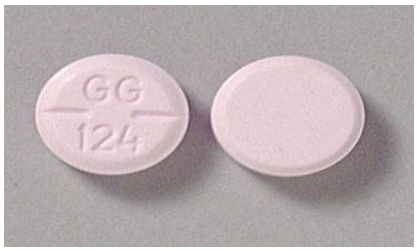
haloperidol	1mgtablet	
haloperidol	2mgtablet	
haloperidol	5mgtablet	
haloperidol	0.5mgtablet	
haloperidol	10mgtablet	
haloperidol	1mgtablet	

haloperidol	20mgtablet	
haloperidol	2mgtablet	
haloperidol	5mgtablet	

OVERDOSE

Manifestations

In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reactions would be manifested by muscular weakness or rigidity and a generalized or localized tremor as demonstrated by the akineticor agitans types respectively. With accidental overdosage, hypertensionrather than hypotension occurred in a two-year old child. The risk of ECGchanges associated with torsade de pointes should be considered.

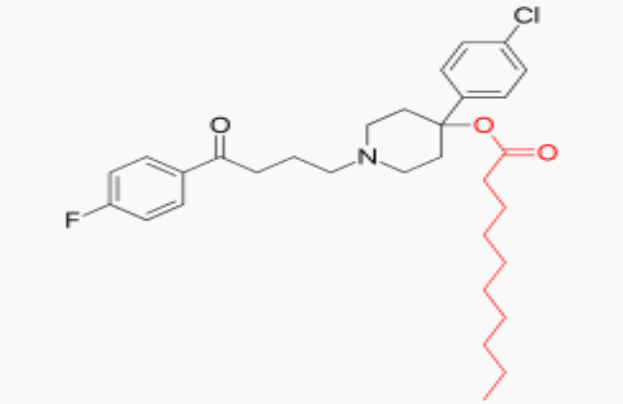
Treatment

Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counteracted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. ECG and vital signs should be monitored especially for signs of Q-T prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

Use caution in patients with severe cardiovascular disorders, because of possibility of transient hypotension and/or precipitation of anginal pain; should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity and paradoxical further lowering of the blood pressure may occur; use metaraminol, phenylephrine or norepinephrine instead.

CHEMISTRY

Use caution in patients receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities; haloperidol may lower convulsive threshold; if indicated, adequate anticonvulsant therapy should be concomitantly maintained.



Skeletal formula of haloperidol decanoate. The decanoate group is highlighted in red.

During long-term treatment of chronic psychiatric disorders, the daily dose should be reduced to the lowest level needed for maintenance of remission. Sometimes, it may be indicated to terminate haloperidol treatment gradually.[25] In addition, during long-term use, routine monitoring including measurement of BMI, blood pressure, fasting blood sugar, and lipids, is recommended due to the risk of side effects.[26]

Other forms of therapy (psychotherapy, occupational therapy/ergotherapy, or social rehabilitation) should be instituted properly. PET imaging studies have suggested low doses are preferable. Clinical response was associated with at least 65% occupancy of D2 receptors, while greater than 72% was likely to cause hyperprolactinaemia and over 78% associated with extrapyramidal side effects. Doses of haloperidol greater than 5 mg increased the risk of side effects without improving efficacy.[27] Patients responded with doses under even 2 mg in first-episode psychosis.[28] For maintenance treatment of schizophrenia, an international consensus conference recommended a reduction dosage by about 20% every 6 months until a minimal maintenance dose is established.[26]

- Depot forms are also available; these are injected deeply intramuscularly at regular intervals. The depot forms are not suitable for initial treatment, but are suitable for patients who have demonstrated inconsistency with oral dosages.

The decanoate ester of haloperidol (haloperidol decanoate, trade names Haldol decanoate, Halomonth, Neoperidole) has a much longer duration of action, so is often used in people known to be noncompliant with oral medication. A dose is given by intramuscular injection once every two to four weeks.[29] The IUPAC name of haloperidol decanoate is [4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl] decanoate.

Topical formulations of haloperidol should not be used as treatment for nausea because research does not indicate this therapy is more effective than alternatives.[30]

SIDE EFFECTS

- dizziness, fainting, fast or pounding heartbeat;
- restless muscle movements in your eyes, tongue, jaw, or neck;
- tremor (uncontrolled shaking);
- seizure (convulsions);
- pale skin, easy bruising or bleeding, flu symptoms;
- very stiff (rigid) muscles, high fever, sweating, confusion, fast or uneven heartbeat

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.

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)[31,32]

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 withanticholinergic drugs.

Body As A Whole

Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with HALDOL.

Hematologic Effects

Reports have appeared citing the occurrence of mild and usually transientleukopenia 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 ofphotosensitivity and loss of hair.

Endocrine Disorders

Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemiaand 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.

Rhabdomyolysis has been reported.[33,34,35,36]

Other considerations

Pregnancy & Lactation

Pregnancy category: C; neonates exposed to antipsychotic drugs during 3rd trimester of pregnancy are at risk for extrapyramidal or withdrawal symptoms after delivery; these complications vary in severity, in some cases being self-limited and in other cases necessitating ICU support and prolonged hospitalization

Lactation: Drug enters breast milk; not recommended

Cautions

Risk of sudden death, torsades de pointes, and prolonged QT interval from off-label IV administration of higher

than recommended dose: monitor ECG if administering IV
Conditions or drugs that prolong QT interval, congenital long QT syndrome
Safety of prolonged administration of 100 mg/day PO not established
Avoid use in narrow angle glaucoma, bone marrow suppression, and severe hypotension
FDA warning regarding off-label use for dementia in elderly[37,38]
Leukopenia/neutropenia and agranulocytosis reported; possible risk factors include preexisting low white blood cell (WBC) count and history of drug-induced leukopenia/neutropenia
If patient has history of clinically significant presence of either risk factor, monitor complete blood count (CBC) frequently during first few months of therapy; discontinue drug at first sign of clinically significant WBC decline <1000/µL in absence of other causative factors, and continue monitoring WBC count until recovery
Severe neurotoxicity manifesting as rigidity or inability to walk or talk may occur in patients with thyrotoxicosis also receiving antipsychotics
If administering IV or IM, watch for hypotension; use with caution in diagnosed CNS depression, subcortical brain damage, or cardiac disease; if history of seizures, benefits must outweigh risks; significant increase in body temperature may indicate intolerance to antipsychotics (discontinue if this occurs)
Use caution in patients at risk of pneumonia (eg, Alzheimer's patients); antipsychotic use reported to be associated with esophageal dysmotility and aspiration
Extrapyramidal symptoms may occur including acute dystonic reactions, akathisia, tardive dyskinesia, and pseudoparkinsonism
Hyperprolactinemia may occur
Monitor for mental status changes, muscle rigidity, fever, and/or autonomic instability; neuroleptic malignant syndrome may occur
May cause orthostatic hypotension
Association with increased risk of pigmentary retinopathy reported
Impairment of core body temperature regulation reported; use caution with activities that may increase body temperature including strenuous exercise, heat exposure, dehydration, and concomitant medications with anticholinergic effects
Caution in patients receiving anticoagulants; isolated instance of interference occurred with effects of one anticoagulant (phenindione)
When used to control mania in cyclic disorders, there may be rapid mood swing to depression
May cause anticholinergic effects; use caution in patients with xerostomia, urinary retention, BPH, decreased gastrointestinal motility, paralytic ileus, or visual problems
May cause CNS depression; may impair ability to operate heavy machinery or driving
Decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation; a number of cases of bronchopneumonia, some fatal, reported; if signs and symptoms appear, especially in the elderly, institute remedial therapy promptly

Patient/Family Teaching

● Advise patient to take medication as directed. Take missed doses as soon as remembered, with remaining doses evenly spaced throughout the day. May require several weeks to obtain desired effects. Do not increase dose or discontinue medication without consulting health care professional. Abrupt withdrawal may cause dizziness; nausea; vomiting; GI upset; trembling; or uncontrolled movements of mouth, tongue, or jaw.
● Inform patient of possibility of extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome. Caution patient to report symptoms immediately.
● Advise patient to change positions slowly to minimize orthostatic hypotension.
● May cause drowsiness. Caution patient to avoid driving or other activities requiring alertness until response to medication is known.
● Caution patient to avoid taking alcohol or other CNS depressants concurrently with this medication.
● Advise patient to use sunscreen and protective clothing when exposed to the sun to prevent photosensitivity reactions. Extremes of temperature should also be avoided; drug impairs body temperatureregulation.
● Instruct patient to use frequent mouth rinses, good oral hygiene, and sugarless gum or candy to minimize dry mouth.
● Advise patient to notify health care professional of medication regimen prior to treatment or surgery.
● Instruct patient to notify health care professional promptly if weakness, tremors, visual disturbances, dark-colored urine or clay-colored stools, sore throat, fever, menstrual abnormalities, galactorrhea or sexual dysfunction occur.
● Emphasize the importance of routine follow-up exams to monitor response to medication and detect side effects.

Evaluation/ Desired Outcomes

● Decrease in hallucinations, insomnia, agitation, hostility, and delusions.
● Decreased tics and vocalization in Tourette's syndrome.
● Improved behavior in children with severe behavioral problems. If no therapeutic effects are seen in 2– 4 wk, dosage may be increased.

CONCLUSION

Haloperidol, which is an old and inexpensive drug, may prove to be an interesting and cost-effective alternative to newer and more costly antiemetics. However, before haloperidol can be recommended for this indication, its antiemetic dose range, minimal effective dose, and adverse effects must be defined. Topical formulations of

haloperidol should not be used as treatment for nausea because research does not indicate this therapy is more effective than alternatives. During long-term treatment of chronic psychiatric disorders, the daily dose should be reduced to the lowest level needed for maintenance of remission. Sometimes, it may be indicated to terminate haloperidol treatment gradually. In addition, during long-term use, routine monitoring including measurement of BMI, blood pressure, fasting blood sugar, and lipids, is recommended due to the risk of side effects.

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