

DRUGDEX-EV 2528

MICROMEDEX

DRUGDEX® Evaluations
Database updated March 2017

MOLINDONE

[Overview](#)
[Dosing Information](#)
[Pharmacokinetics](#)
[Cautions](#)
[Clinical Applications](#)
[References](#)

0.0] Overview

1] Class

a) This drug is a member of the following class(es):

Antipsychotic

2] Dosing Information

a) [Molindone](#) Hydrochloride

1] Adult

a) [Schizophrenia](#)

1) Initial, 50 to 75 mg/day orally; increase to 100 mg/day in 3 or 4 days; titrate up or down depending on severity of symptoms and patient response; 225 mg/day may be required for patients with severe symptoms [2]

2) Maintenance, 5 to 15 mg orally 3 or 4 times daily for mild symptoms; 10 to 25 mg 3 or 4 times daily for moderate symptoms; 225 mg/day may be required for severe symptoms [2]

2] Pediatric

a) [Schizophrenia](#)

1) (12 years or older) Initial, 50 to 75 mg/day orally; increase to 100 mg/day in 3 or 4 days; titrate up or down depending on severity of symptoms and patient response; 225 mg/day may be required for patients with severe symptoms [2]

2)) (12 years or older) Maintenance, 5 to 15 mg orally 3 or 4 times daily for mild symptoms; 10 to 25 mg 3 or 4 times daily for moderate symptoms; 225 mg/day may be required for severe symptoms [2]

3)) Contraindications

a)) Molindone Hydrochloride

- 1)) Comatose states[2]
- 2)) Hypersensitivity to molindone [2]
- 3)) Severe central nervous system depression (eg alcohol, barbiturates, narcotics)[2]

4)) Serious Adverse Effects

a)) Molindone Hydrochloride

- 1)) Leukopenia
- 2)) Neuroleptic malignant syndrome
- 3)) Neutropenia
- 4)) Seizure
- 5)) Tardive dyskinesia

5)) Clinical Applications

a)) Molindone Hydrochloride

- 1)) FDA Approved Indications
 - a)) Schizophrenia

1.0) Dosing Information

[Drug Properties](#)
[Storage and Stability](#)
[Adult Dosage](#)
[Pediatric Dosage](#)

1.1) Drug Properties

A)) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B)) Synonyms

[Molindone](#)
[Molindone HCl](#)
[Molindone Hydrochloride](#)

C) Physicochemical Properties**1) Molecular Weight****a)** 312.84**2) pKa****a)** 6.94**1.2) Storage and Stability****A) Oral route****1) Tablet**

a) Molindone tablets are visually compatible when mixed with lithium citrate syrup (5 and 10 mL) [99].

b) Store molindone tablets at room temperature (59 to 86 degrees Fahrenheit or 15 to 30 degrees Celsius) and protect from light [100].

1.3) Adult Dosage**1.3.1) Normal Dosage****1.3.1.A) Important Note**

j) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

1.3.1.B) Molindone Hydrochloride**1.3.1.B.1) Oral route****1.3.1.B.1.a) Schizophrenia**

1) Initial dosage: 50 to 75 mg/day orally; increase to 100 mg/day in 3 or 4 days [2]

2) Dosage titration: Titrate up or down depending on severity of symptoms and patient response; 225 mg/day may be required for patients with severe symptoms [2].

3) Maintenance dosage: 5 to 15 mg orally 3 or 4 times daily for mild symptoms; 10 to 25 mg 3 or 4 times daily for moderate symptoms; 225 mg/day may be required for severe symptoms [2]

1.3.4) Dosage in Geriatric Patients**A) Molindone Hydrochloride**

1) Initiate therapy at a lower dosage in elderly and debilitated patients [2].

1.3.6) Dosage in Other Disease States**A) Molindone Hydrochloride**

1) Debilitated

- a) Initiate therapy at a lower dosage in debilitated patients [2].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Important Note

- j) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

1.4.1.B] Molindone Hydrochloride

1.4.1.B.1] Oral route

1.4.1.B.1.a] Schizophrenia

- 1) Initial dosage (12 years or older): 50 to 75 mg/day orally; increase to 100 mg/day in 3 or 4 days [2]
2) Dosage titration (12 years or older): Titrate up or down depending on severity of symptoms and patient response; 225 mg/day may be required for patients with severe symptoms [2].
3) Maintenance dosage (12 years or older): 5 to 15 mg orally 3 or 4 times daily for mild symptoms; 10 to 25 mg 3 or 4 times daily for moderate symptoms; 225 mg/day may be required for severe symptoms [2]

1.4.5] Dosage in Other Disease States

A) Molindone Hydrochloride

1) Debilitated

- a) Initiate therapy at a lower dosage in debilitated patients [2].

2.0] Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1] Onset and Duration

A) Onset

1) Initial Response

- a) DEPRESSION: ORAL, 24 to 36 hours (Simpson, 1971).

B) Duration

1) Single Dose

- a) Antipsychotic effects, oral: 24 to 36 hours [94].

2.2] Drug Concentration Levels

A) Time to Peak Concentration

- 1) ORAL: 1.5 hours [94].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

- 1) INTRAMUSCULAR: the intramuscular form is approximately 1.5 times more bioavailable than the oral form [96].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

- 1) Liver [94].

B) Metabolites

- 1) There are 36 recognized metabolites of [MOLINDONE](#) [94].

2.3.4] Excretion

A) Kidney

- 1) Renal Excretion (%)

- a) 2% or less of an administered dose is excreted unchanged in the urine [94].

2.3.6] Extracorporeal Elimination

A) [Hemodialysis](#)

- 1) Dialyzable: No[94]

B) Peritoneal

- 1) Dialyzable: No[94]

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.0.A] Black Box WARNING

Molindone Hydrochloride

Oral (Tablet)

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. Analyses of seventeen placebo-controlled trials (model duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) to the patients is not clear. Molindone is not approved for the treatment of patients with dementia-related psychosis. [2]

3.1] Contraindications

A) Molindone Hydrochloride

- 1) Comatose states[2]
- 2) Hypersensitivity to molindone [2]
- 3) Severe central nervous system depression (eg alcohol, barbiturates, narcotics)[2]

3.2] Precautions

A) Molindone Hydrochloride

- 1) Black Box Warning: Elderly patients with dementia related psychosis receiving antipsychotics (unapproved use) may be at an increased risk for death [2]
- 2) Beers Criteria: Avoid use for behavioral problems of dementia or delirium (unless nonpharmacological measures fail and the patient is a threat to self or others), as antipsychotics may increase risk of cerebrovascular accident and mortality in patients with dementia. Avoid use in patients with Parkinson Disease as dopamine receptor antagonists may potentially worsen symptoms, and in patients with a history of falls or fractures (unless safer alternatives are not available), or cognitive impairment as it may cause adverse CNS effects, syncope, ataxia, and impaired psychomotor performance. If prescribed in older adults, use caution as SIADH or hyponatremia may occur or worsen; monitor sodium levels when starting or changing doses [1].
- 3) Concomitant Use: Contains calcium sulfate; may interfere with absorption of phenytoin sodium or tetracyclines [2]
- 4) Neurologic: Tardive dyskinesia may occur; increased risk in the elderly (especially elderly women) and with prolonged use and/or higher cumulative doses; minimizing dosing and duration of use to clinical response is recommended; consider discontinuation if suspected[2]
- 5) Neurologic: May cause drowsiness or hyperactivity [2]
- 6) Neurologic: Convulsive seizures have been reported [2]

7)) Neurologic: Antiemetic effects may obscure signs of [brain tumor](#) [2]

8)) Gastrointestinal: Antiemetic effects may obscure signs of [intestinal obstruction](#) [2]

9)) Endocrine and Metabolic: Elevations in prolactin levels have been reported and have been associated with [galactorrhea](#), [amenorrhea](#), [gynecomastia](#) and impotence; consider risks and benefits of use in patients with a history of [breast cancer](#), as some human [breast cancers](#) may be prolactin dependant [2]

10)) [Neuroleptic Malignant Syndrome](#): Potentially fatal [neuroleptic malignant syndrome](#) has been reported; immediate discontinuation and intensive symptomatic treatment required; consider risks and benefits prior to restarting treatment [2]

11)) Hematologic: [Leukopenia](#), [neutropenia](#), and [agranulocytosis](#) have been reported; increased risk in patients with pre-existing [leukopenia](#) or drug induced [leukopenia](#); monitoring recommended and discontinuation may be required [2]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Molindone](#) Hydrochloride

3.3.1.A.1] [Electrocardiogram](#) abnormal

a)) Incidence: Rare [2].

b)) Adult Clinical Trials

1)) Transient, nonspecific T-wave changes have been reported rarely on ECG [2].

3.3.1.A.2] Hypotension

a)) Incidence: Rare [2].

b)) Adult Clinical Trials

1)) Significant hypotension has been reported rarely [2].

3.3.1.A.3] [Tachycardia](#)

a)) Incidence: Occasionally [2].

b)) Adult Clinical Trials

1)) Has been reported occasionally [2].

3.3.2] Dermatologic Effects

3.3.2.A] [Molindone](#) Hydrochloride

3.3.2.A.1] Rash

a)) Incidence: Occasionally [2].

b)) Adult Clinical Trials

1)) Nonspecific skin rash has been reported occasionally [2].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Molindone Hydrochloride

3.3.3.A.1] Abnormal weight loss

a) Adult Clinical Trials

1) Has been reported [2]

2) Weight loss of 10 to 24 pounds was reported in 5 patients who received the drug in dosages ranging from 5 to 200 mg/day for up to 19 months [9].

3.3.3.A.2] Disorder of acid-base balance

a) Adult Case Report

1) Shallow, rapid respirations occurred with therapeutic use, secondary to [metabolic acidosis](#), in a patient with probable [neuroleptic malignant syndrome](#) who had been previously exposed to other neuroleptics. [Metabolic acidosis](#) occurred in a patient therapeutically treated with [molindone](#) who developed [rhabdomyolysis](#) and [renal failure](#) [8].

3.3.3.A.3] Disorder of fluid AND/OR electrolyte

a) Adult Case Report

1) Hyperkalemia, hyperphosphatemia and [hypocalcemia](#) occurred in a patient therapeutically treated with [molindone](#) who developed [renal failure](#) and [rhabdomyolysis](#) .[8]

3.3.3.A.4] Galactorrhea

a) Incidence: Infrequently [2]

b) Adult Clinical Trials

1) Has been reported infrequently [2]

c) Adult Case Report

1) [Molindone](#) was discontinued when a patient experienced [galactorrhea](#). When [molindone](#) therapy was reinstituted, [galactorrhea](#) recurred but was not accompanied by [hyperprolactinemia](#). [Galactorrhea](#) persisted throughout a 2-year course of therapy and ceased upon discontinuation of therapy [10].

3.3.3.A.5] Gynecomastia

a) Incidence: Infrequently [2]

b) Adult Clinical Trials

1) Has been reported infrequently [2]

3.3.3.A.6] Metabolic syndrome

See Drug Consult reference: Antipsychotic Agents - [Metabolic Syndrome](#)

3.3.4] Gastrointestinal Effects

3.3.4.A] Molindone Hydrochloride**3.3.4.A.1] Constipation****a) General Information**

- 1) May occur if used to treat extrapyramidal symptoms [2].

3.3.4.A.2] Excessive salivation**a) Incidence: Occasionally [2].****b) Adult Clinical Trials**

- 1) Salivation has been reported occasionally [2].

3.3.4.A.3] Nausea**a) Incidence: Occasionally [2].****b) Adult Clinical Trials**

- 1) Has been reported occasionally [2]

3.3.4.A.4] Xerostomia**a) Incidence: Occasionally [2].****b) Adult Clinical Trials**

- 1) Dry mouth has been reported occasionally [2]

3.3.5] Hematologic Effects**3.3.5.A] Molindone Hydrochloride****3.3.5.A.1] Agranulocytosis****a) Adult Case Report**

- 1) A 64-year-old woman receiving long-term [clozapine](#) therapy and short-term [molindone](#) therapy developed [agranulocytosis](#) and an elevated temperature. The patient was treated with [filgrastim](#) 300 mcg/day and responded with an increased absolute neutrophil count, which exceeded 500 X 10(6) per liter at day seven [3].

3.3.5.A.2] Leukocytosis**a) Incidence: Rarely [2]****b) Adult Clinical Trials**

- 1) Has been reported rarely [2]

c) Management

- 1) If occurs, may continue therapy if symptoms are not present [2].

3.3.5.A.3] Leukopenia**a) Incidence: Rarely [2]**

b) General Information

1) A known class effect temporally related to antipsychotic agents [2]

2) Possible increased risk with preexisting low WBC count and history of drug-induced [leukopenia](#) [2]

c) Adult Clinical Trials

1) Has been reported rarely [2]

d) Management

1) Monitoring recommended and discontinuation of therapy may be warranted [2]

2) If occurs, may continue therapy if symptoms are not present [2].

3.3.5.A.4] [Neutropenia](#)**a) General Information**

1) A known class effect temporally related to antipsychotic agents [2]

2) Possible increased risk with preexisting low WBC count and history of drug-induced [neutropenia](#) [2]

b) Management

1) If clinically significant [neutropenia](#) occurs, monitor carefully for fever or other signs of infection and treat promptly [2].

2) If severe [neutropenia](#) occurs (absolute neutrophil count less than 1000/mm(3)), discontinue treatment and measure WBC until recovery [2].

3.3.6] Hepatic Effects**3.3.6.A] [Molindone](#) Hydrochloride****3.3.6.A.1] [Abnormal liver function](#)**

a) Incidence: Rare [2]

b) Adult Clinical Trials

1) Clinically significant alterations in liver function have been reported rarely [2]

3.3.6.A.2] [Hepatotoxicity](#)**a) Case Report**

1) [Hepatotoxicity](#) was described in a 17-year-old male following [molindone](#) therapy for approximately 5 weeks. Withdrawal of the drug resulted in resolution of hepatic function test abnormalities. The patient was rechallenged with [molindone](#) resulting in similar increases in hepatic function tests [11].

3.3.8] Musculoskeletal Effects**3.3.8.A] [Molindone](#) Hydrochloride**

3.3.8.A.1] Decreased bone mineral density**a)] General Information**

1)] Most likely due to persistent hyperprolactinemia during use [12]

b)] Adult Clinical Trials

1)] Schizophrenia or schizoaffective disorder: Regardless of treatment duration, 23% of women and 31% of men receiving risperidone or a conventional antipsychotic, including molindone, had low bone mineral density; while 61% of women and 43% of men had hyperprolactinemia. After controlling for age, low bone mineral density was associated with hyperprolactinemia in men, but not in women [12]

3.3.8.A.2] Rhabdomyolysis**a)] Adult Case Report**

1)] Rhabdomyolysis occurred in a 32-year-old male patient 3 days into a course of molindone 100 mg/day. Previous therapy with several other psychotherapeutic drugs had not been associated with this adverse effect. No other changes in drug therapy were temporally associated with the effect. The patient required several courses of dialysis for rhabdomyolysis-induced acute renal failure and eventually recovered [8].

3.3.9] Neurologic Effects**3.3.9.A] Molindone****3.3.9.A.1] Extrapyramidal sign**

See Drug Consult reference: Neuroleptic-Induced Extrapyramidal Reactions

3.3.9.A.2] Seizure

See Drug Consult reference: Antipsychotics - Effect on Seizure Threshold

3.3.9.B] Molindone Hydrochloride**3.3.9.B.1] Akathisia****a)] General Information**

1)] Motor restlessness may occur early in susceptible individuals [2]

2)] Typically reversible with appropriate management [2]

3.3.9.B.2] Akinesia**a)] General Information**

1)] Characterized by tremor, rigidity, immobility, and reduction of voluntary movements [2]

2)] Typically reversible with appropriate management [2]

b)] Adult Clinical Trials

1)] Has been reported [2]

3.3.9.B.3] Dystonia**a) General Information**

- 1) A known antipsychotic drug class effect occurring during the first few days of treatment [2]
- 2) Increased risk in men and younger patients [2]
- 3) Symptoms may occur with low doses, but are more common and severe with larger doses [2].
- 4) Symptoms include neck muscle spasm (sometimes progressing to throat tightness), tongue protrusion, and difficulty breathing or swallowing [2].

3.3.9.B.4] Neuroleptic malignant syndrome**a) General Information**

- 1) A known class effect related to antipsychotic agents [2][2]
- 2) Can manifest clinically with [hyperpyrexia](#), muscle rigidity, altered mental status, and autonomic instability such as irregular pulse or blood pressure, [tachycardia](#), diaphoresis, and [cardiac dysrhythmias](#) [2]

b) Management

- 1) If occurs, immediately discontinue all antipsychotic and nonessential medications, initiate intensive symptomatic treatment and medical monitoring, and treat any concomitant serious medical problems [2].
- 2) If reinitiating therapy, monitor carefully for recurrence [2].

c) Adult Case Reports

- 1) [Neuroleptic malignant syndrome](#) (NMS) possibly caused by [molindone](#) was reported to occur in a 40-year-old woman with a past history of NMS due to [molindone](#). The patient had received [lithium](#) 300 mg in the morning and 600 mg at bedtime and [chlorpromazine](#) 200 mg at bedtime for one week with no signs of improvement. Her medications were stopped and the next morning she received [molindone](#) 25 mg. By that afternoon she was febrile (temperature 40 degrees Celsius), rigid, and diaphoretic with a CPK of 1430 units/L. All medications were stopped and the patient was started on [bromocriptine](#). Within 48 hours, she was afebrile and her CPK had fallen to 300 units/L [6].
- 2) [Neuroleptic malignant syndrome](#) (NMS) possibly resulting from [molindone](#) was reported in a 36-year-old woman receiving [haloperidol](#), [chlorpromazine](#), and [molindone](#). The patient made a full recovery upon discontinuation of the neuroleptics [7].

3.3.9.B.5] Seizure**a) Adult Clinical Trials**

- 1) Convulsive seizures has been reported in a few instances [2]

3.3.9.B.6] Somnolence

a) Incidence: Most frequently [2]

b) General Information

1) Generally subsides with continued use or with dosage reduction [2]

c) Adult Clinical Trials

1) Has been reported most frequently [2]

3.3.9.B.7] Tardive dyskinesia

a) General Information

1) A known class effect related to antipsychotic agents [2]

2) May appear during therapy or upon discontinuation, and (less commonly) after brief treatment periods at low doses [2]

3) Reversible or irreversible [2]

4) May remit partially or completely upon discontinuation [2]

5) May be related to the duration of treatment and the cumulative dose [2]

6) Antipsychotics may mask the underlying disease by suppressing the signs and symptoms of the syndrome [2].

7) Prevalence appears to be highest among the elderly, especially elderly women [2].

b) Management

1) If symptoms occur, consider discontinuation [2].

c) Adult Case Reports

1) A case of **tardive dyskinesia** associated with **molindone** was reported in a 29-year-old female who had received numerous antipsychotic drugs prior to initiation of **molindone**. During the third month of treatment with **molindone**, she developed symptoms of **tardive dyskinesia**. Three months after discontinuation of the drug, the symptoms were subsiding and she was transferred to outpatient care [4].

2) **Tardive dyskinesia** occurred in a 27-year-old man who, prior to **molindone**, had received **haloperidol**, **trifluoperazine**, and **fluphenazine** in short courses without symptoms. **Dyskinesia** developed 10 months after institution of **molindone** therapy and had persisted for 7 months at the time of the report [5].

3.3.10] Ophthalmic Effects

3.3.10.A] Molindone Hydrochloride

3.3.10.A.1] Blurred vision

a) Incidence: Occasionally [2].

b) Adult Clinical Trials

1) Has been reported occasionally [2]

3.3.12] Psychiatric Effects**3.3.12.A] Molindone Hydrochloride****3.3.12.A.1] Depression****a) Adult Clinical Trials**

1) Has been reported [2]

3.3.12.A.2] Euphoria**a) Adult Clinical Trials**

1) Has been reported [2]

3.3.12.A.3] Hyperactive behavior**a) Adult Clinical Trials**

1) Has been reported [2]

3.3.13] Renal Effects**3.3.13.A] Molindone Hydrochloride****3.3.13.A.1] Acute renal failure****a) Adult Case Report**

1) Hyperkalemia, hyperphosphatemia, and hypocalcemia occurred in a patient therapeutically treated with molindone who developed renal failure and rhabdomyolysis [8].

3.3.13.A.2] Urinary retention**a) General Information**

1) May occur if used to treat extrapyramidal symptoms [2].

3.3.14] Reproductive Effects**3.3.14.A] Molindone Hydrochloride****3.3.14.A.1] Amenorrhea****a) Incidence: Infrequently [2]****b) General Information**

1) May be reversible [2]

c) Adult Clinical Trials

1) Has been reported infrequently [2]

3.3.14.A.2] Disorder of menstruation**a) Adult Case Reports**

1)) Menstrual abnormalities were reported in 10 patients receiving [molindone](#) (25 to 150 mg/day) over a period of 6 weeks. Heavy menstrual flow which was not evident prior to therapy occurred in 4 of the patients. One patient developed [amenorrhea](#) [13].

3.3.14.A.3] Increased libido

a)) Adult Clinical Trials

1)) Has been reported [2]

3.3.14.A.4] [Priapism](#)

a)) Adult Case Report

1)) One patient experienced [priapism](#) requiring surgery, resulting in residual impairment of erectile function [2].

3.3.16] Other

3.3.16.A] [Molindone Hydrochloride](#)

3.3.16.A.1] Death

a)) Adult Clinical Trials

1)) Results of a population-based, retrospective cohort study demonstrated that the use of conventional antipsychotics was associated with an even greater risk for death than atypical antipsychotics when administered to elderly patients (aged 66 years and older) with [dementia](#). Atypical versus no antipsychotic use and conventional versus atypical antipsychotic use pair-wise comparisons were made. A total of 27,259 matched pairs were identified and the [dementia](#) cohort was stratified based on place of residence (community versus long-term care facilities). In order to adjust for difference in baseline health status, propensity score matching was used. The primary outcome of the study was all-cause mortality. The risk for death was evaluated at 30, 60, 120, and 180 days after the antipsychotic medications were initially dispensed. There was a statistically significant increase in the risk for death at 30 days associated with new use of atypical antipsychotic medications compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio (HR), 1.31 (95% confidence interval (CI), 1.02 to 1.70); absolute risk difference, 0.2 percentage point) and long-term care cohort (adjusted HR, 1.55 (95% CI, 1.15 to 2.07); absolute risk difference, 1.2 percentage points). For both cohorts, the risk associated with atypical antipsychotics appeared to persist to 180 days. The risk for death associated with conventional antipsychotics was even greater than the risk identified with atypical antipsychotics. At 30 days, the adjusted HR for the community-dwelling cohort was 1.55 (95% CI, 1.19 to 2.02) and 1.26 (95% CI, 1.04 to 1.53) for the long-term care cohort (adjusted risk difference for both was 1.1 percentage points). The risk appeared to persist to 180 days for both groups. Some important limitations to the study include unknown or unmeasured confounders may influence the results and cause of death could not be examined [14].

2)) Results of a population-based, retrospective cohort study demonstrated comparable to possibly greater risk of death associated with the use of conventional antipsychotic medications in the elderly (aged 65 years and older) compared with atypical antipsychotic medications. The analysis excluded patients with [cancer](#) and included only new users of

antipsychotic medications. The primary study outcome was 180-day all-cause mortality. A set of potential confounders was measured based on healthcare utilization data within 6 months before the initiation of antipsychotic medications. Of the 37,241 elderly patients identified, 12,882 and 24,359 received conventional and atypical antipsychotic medications, respectively. The risk of death in the conventional drug group within the first 180 days was 14.1% compared with 9.6% in the atypical drug group (unadjusted mortality ratio, 1.47; 95% confidence interval (CI), 1.39 to 1.56). In the multi-variable analysis which controlled for potential confounders, the adjusted mortality ratio for the risk of death within 180 days for conventional versus atypical drug therapy was 1.32 (95% CI, 1.23 to 1.42). When the most frequently prescribed conventional antipsychotic drugs were compared with [risperidone](#), the mortality ratio associated with [haloperidol](#) was 2.14 (95% CI, 1.86 to 2.45) and [loxapine](#) was 1.29 (95% CI, 1.19 to 1.40), while there was no difference associated with [olanzapine](#). The increased mortality risk for conventional versus atypical drug therapy was greatest when doses higher (above median) doses were used (mortality ratio 1.67; 95% CI, 1.5 to 1.86) and also during the first 40 days of therapy (mortality ratio 1.6; 95% CI, 1.42 to 1.8). Confirmatory analyses consisting of multi-variable Cox regression, propensity score, and instrumental variable estimation confirmed the results of the study [15].

3J) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.5 years). A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all timepoints studied after beginning therapy (within 180 days: RR, 1.37; 95% CI=1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI=1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI=1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI=1.14 to 1.41). In addition, the adjusted risks of death observed in patients with [dementia](#) (RR, 1.29; 95% CI=1.15 to 1.45), without [dementia](#) (RR, 1.45; 95% CI=1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI=1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI=1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI=1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided [16].

3.4J Teratogenicity/Effects in Pregnancy/Breastfeeding

AJ) Teratogenicity/Effects in Pregnancy

1J) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

aJ) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2J) Crosses Placenta: Unknown

3J) Clinical Management

a)) There are no adequate and well-controlled studies of [molindone](#) use in pregnant women; however, third-trimester antipsychotic drug exposure has been associated with extrapyramidal and/or withdrawal symptoms in neonates. In animal studies, there was no evidence of [teratogenicity](#) in pregnant rats, mice, or rabbits administered oral [molindone](#). [Molindone](#) should be given during pregnancy only if the potential benefit to the mother outweighs the potential [risk to the fetus](#) [92].

4)) Literature Reports

a)) Maternal use of antipsychotic drugs during the third trimester of pregnancy has been associated with an increased risk of neonatal extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) following delivery. Severity of these adverse effects have ranged from cases that are self-limiting to cases that required prolonged periods of hospitalization and ICU care [92].

b)) One patient received [molindone](#) throughout the entire pregnancy and delivered normal twins. Immediate post-birth examination revealed no detectable adverse effects secondary to the maternal ingestion of [molindone](#) during pregnancy despite the fact that a total dose of 9.8 grams was ingested [93].

B)) Breastfeeding

1)) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a)) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2)) Clinical Management

a)) No reports describing the use of [molindone](#) during human lactation are available and the effects on the nursing infant from exposure to the drug in milk are unknown [92].

3.5) Drug Interactions

3.5.1) Drug-Drug Combinations

3.5.1.A) [Alfentanil](#)

1)) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2)) Summary: The concomitant use of [alfentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Reserve concomitant use of [alfentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce

the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

7J) Probable Mechanism: additive CNS depression

3.5.1.BJ Belladonna

1J) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2J) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [molindone](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[90]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [molindone](#) is unknown. Caution is advised.

3J) Severity: minor

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.

7J) Probable Mechanism: additive anticholinergic effect

3.5.1.CJ Belladonna Alkaloids

1J) Interaction Effect: excessive anticholinergic activity (severe dry mouth, constipation, decreased urination, excessive sedation, blurred vision)

2J) Summary: The anticholinergic activity of the active alkaloids present in belladonna may predispose the patient to excessive anticholinergic activity if taken with [molindone](#). Belladonna contains L-hyoscyamine, [atropine](#), and [scopolamine](#) with a total alkaloid content of at least 0.3% in the leaves and 0.5% in the roots[90]. Because belladonna is typically available as a homeopathic preparation, the clinical severity of the interaction with [molindone](#) is unknown. Caution is advised.

3J) Severity: minor

4J) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Excessive anticholinergic activity may be manifested by dry mouth, constipation, urinary retention, [tachycardia](#), decreased sweating, mydriasis, blurred vision, elevated temperature, muscular weakness, and sedation. If such effects are noted, belladonna should be discontinued immediately. In severe cases, [paralytic ileus](#), confusion, [psychoses](#), agitation, delusions, [delirium](#), and paranoia may be encountered as well as [tachycardia](#), [dysrhythmia](#), and [hypertension](#). In severe cases, immediate medical attention should be obtained.

7J) Probable Mechanism: additive anticholinergic effect

3.5.1.DJ Betel Nut

1J) Interaction Effect: increased extrapyramidal side effects of [molindone](#) (difficulty with movement or abnormal movement of muscles)

2J) Summary: Case reports have described increased extrapyramidal side effects when betel nut was chewed by patients taking [fluphenazine](#) and flupenthixol for [schizophrenia](#)[50]. The extrapyramidal effects were not improved with anticholinergic therapy with [procyclidine](#), and resolved with betel nut

discontinuation [50]. A similar effect may occur if betel nut is chewed with concomitant [molindone](#) therapy. The cholinergic activity of betel nut has been attributed to the arecoline content. When given with peripheral anticholinergics, arecoline increased the heart rate due to central muscarinic agonist activity [51]. Case reports suggest the onset of betel nut activity to be within 3 weeks with resolution within 4 to 7 days after discontinuation [50].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: It is unclear to what extent the cholinergic effect of betel nut may increase the incidence of extrapyramidal side effects of [molindone](#), especially if patients are treated with anticholinergic agents to control these side effects. Deterioration in symptoms of patients with [Parkinson's disease](#) or other extrapyramidal movement disorders may be expected. Persons who have been chewing betel nut have a characteristic red stain on the teeth which may help the clinician discover betel nut use.

7) Probable Mechanism: cholinergic effect of betel nut

8) Literature Reports

a) Within 3 weeks of initiating betel nut chewing, a 51-year-old Indian man experienced marked rigidity, bradykinesia, and jaw tremor. This patient had been stabilized for the previous 2 years on [fluphenazine](#) decanoate depot 50 milligrams (mg) every 3 weeks for [schizophrenia](#) and [procyclidine](#) 5 mg twice daily for a mild Parkinsonian tremor. Within one week of discontinuation of betel nut chewing, the patient's condition returned to baseline. This report appears to demonstrate decreased anticholinergic effects of [procyclidine](#) when coadministered with betel nut [46].

b) Following betel nut ingestion, a 45-year-old Indian man developed [akathisia](#), tremor and stiffness which was not affected by dosage escalations of up to 20 mg daily of [procyclidine](#). This patient had been previously stabilized on flupenthixol 60 mg depot every two weeks for the previous year for [schizoaffective disorder](#) without extrapyramidal side effects. His symptoms resolved over 4 days after discontinuing betel nut. It appears that the anticholinergic effects of [procyclidine](#) were diminished when betel nut was chewed concomitantly [46].

c) High doses (5 mg, 10 mg, and 20 mg) of subcutaneous (SC) arecoline given one hour after SC administration of 0.5 mg of the peripheral anticholinergic agent [methscopolamine](#) increased the heart rate and blood pressure of six patients with [Huntington's disease](#). Significant increases in blood pressure occurred at doses of 5 mg, 10 mg (p less than 0.01) and 20 mg (p less than 0.05). Heart rate increased at doses of 5 mg and 20 mg (p less than 0.01), and 10 mg (p less than 0.05). Subjective effects in some patients included tremor, flushing or pallor at the time of peak drug effect and nausea, weakness, and mental changes at the higher doses. No peripheral cholinergic effects were noted. The results indicated a central muscarinic effect for arecoline [47].

d) A low dose (0.5 mg) of arecoline given intravenously 3 minutes after the peripheral anticholinergic agent [glycopyrrolate](#) 0.15 mg to 8 patients with [major depressive disorder](#) increased their heart rates. The peak heart rate increase in a non-REM portion of the sleep cycle during the 10 minute post-infusion period was 6.75 +/- 12.9 beats per minute for placebo and 25 +/- 10.3 beats per minute for arecoline. The peak heart rates all began 1 to 8 minutes after the arecoline infusion, and the mean heart rate was significantly elevated over placebo from 2 to 10 minutes after arecoline infusion (p less than 0.05) [48].

e) Though chewing betel nut alone does not significantly increase catecholamine levels, a popular betel nut preparation does. Six to eight minutes after chewing betel nut, 4 subjects had only a moderate increase in plasma noradrenaline from 266.2 +/- 105.7 picograms/milliliter (pg/mL) to 313.7 +/- 92.9 pg/mL (p equal to 0.0607). Combining betel nut with lime, catechu and Piper betel

flower as is commonly done caused significant elevation of [norepinephrine](#) in nine subjects from 292.2 +/- 59.5 pg/mL to 375.1 +/- 130.0 pg/mL (p equal to 0.0244) and [epinephrine](#) from 62.5 +/- 23.9 pg/mL to 102.2 +/- 45.0 pg/mL (p equal to 0.0226). In this group [dopamine](#) was also elevated in 8 of 9 subjects, but the mean was not significant [49].

3.5.1.E] [Bromazepam](#)

- 1) Interaction Effect: increased risk of respiratory or cardiovascular depression
- 2) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[45].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[45].
- 7) Probable Mechanism: additive CNS depression

3.5.1.F] [Bromopride](#)

- 1) Interaction Effect: increased risk of extrapyramidal reactions
- 2) Summary: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[25].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of bromopride and other drugs that may cause extrapyramidal reactions is contraindicated[25].
- 7) Probable Mechanism: additive extrapyramidal side effects

3.5.1.G] [Buprenorphine](#)

- 1) Interaction Effect: increased risk of [respiratory depression](#)
- 2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[30][31] and monitor for signs of [respiratory depression](#), sedation, and hypotension [30].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[30][31] and monitor for signs of [respiratory depression](#), sedation, and hypotension [30].
- 7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.H] [Butorphanol](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: The concomitant use of [butorphanol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [butorphanol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

7J) Probable Mechanism: additive CNS depression

3.5.1.IJ [Codeine](#)

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: The concomitant use of [codeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[62].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [codeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[62].

7J) Probable Mechanism: additive CNS depression

3.5.1.JJ [Dehydroepiandrosterone](#)

1J) Interaction Effect: reduced effectiveness of [molindone](#)

2J) Summary: Dehydroepiandrosterone (DHEA) levels within the normal range of 100 to 400 microgram/deciliter (mcg/dL) are conducive to optimal treatment of patients with [psychosis](#)[64]. In case reports, patients have been resistant to antipsychotics when DHEA levels were elevated [64]. Patient being treated with [molindone](#) should avoid DHEA supplementation.

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and [molindone](#). If DHEA is elevated, treatment with [dexamethasone](#) 1 mg orally per day may be used to normalize DHEA levels.

7J) Probable Mechanism: elevated dehydroepiandrosterone (DHEA) blood levels may reduce responsiveness to [molindone](#)

8J) Literature Reports

a)) A 24-year-old female diagnosed with [schizophrenia](#) was resistant to daily doses of [haloperidol](#) 20 milligrams (mg), [fluphenazine](#) 40 mg, [lithium](#) carbonate 1200 mg, and [lithium](#) carbonate 900 mg plus [thioridazine](#) 300 mg. The patient appeared Cushingoid with moon face, acne, facial hair, abdominal hair, and a 40 pound weight gain in the previous 8 months. Dehydroepiandrosterone (DHEA) measured as part of an endocrine panel was 725 micrograms/deciliter (mcg/dL) (normal: 100 to 400 mcg/dL). [Dexamethasone](#) 1 mg orally at bedtime resulted in substantial improvement within one week. The patient appeared calmer, more alert with improved psychotic symptoms and ability to concentrate. At two weeks, a repeated DHEA level was within normal range (328 mcg/dL). The author concluded that elevated DHEA levels were associated with severe [psychosis](#) resistant to conventional antipsychotic therapy [63].

b)) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accompanied by heavy use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusional thinking, auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combativeness. He was diagnosed with [chronic paranoid schizophrenia](#); [schizophrenia](#), chronic undifferentiated type, and [schizoaffective disorder](#), excited type. He was resistant to daily doses of [trifluoperazine](#) 40 mg, [chlorpromazine](#) 400 mg, and [imipramine](#) 100 mg. He was also resistant to combination therapy with [chlorpromazine](#) 400 mg with [thiothixene](#) 80 mg, [thioridazine](#) 1000 mg, [perphenazine](#) 48 mg with [lithium](#) carbonate 1200 mg, [clonazepam](#) 4 mg, and [carbamazepine](#) 1200 mg daily. Baseline DHEA level exceeded 900 mcg/dL. A seven-day suppression test with [dexamethasone](#) 1 mg orally at bedtime resulted in a normal DHEA level of 200 mcg/dL. By day 5, [psychosis](#) improved and the patient was well-oriented, conversational, and was making good eye contact. Once [dexamethasone](#) was discontinued, rapid decompensation and florid [psychosis](#) ensued despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author concluded that elevated DHEA levels were associated with florid [psychosis](#) resistant to conventional antipsychotic therapy [63].

3.5.1.K] [Dihydrocodeine](#)

- 1)) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2)) Summary: The concomitant use of [dihydrocodeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[62].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Reserve concomitant use of [dihydrocodeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[62].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.L] [Doxylamine](#)

- 1)) Interaction Effect: increased risk of CNS depression

- 2) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[37][38]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[37][38]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 7) Probable Mechanism: additive CNS depression

3.5.1.M] [Droperidol](#)

- 1) Interaction Effect: an increased risk of [cardiotoxicity](#) (QT prolongation, [torsades de pointes](#), [cardiac arrest](#))
- 2) Summary: Any drug known to have the potential to prolong the QT interval should not be used together with [droperidol](#). Possible pharmacodynamic interactions can occur between [droperidol](#) and potentially arrhythmogenic agents such as neuroleptics that prolong the QT interval[44].
- 3) Severity: contraindicated
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: The concurrent administration of [droperidol](#) and agents that prolong the QT interval, such as neuroleptics, is contraindicated.
- 7) Probable Mechanism: additive cardiac effects

3.5.1.N] [Fentanyl](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[69]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [70]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [69].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[69].
- 7) Probable Mechanism: additive CNS depression

3.5.1.O] [Flibanserin](#)

- 1) Interaction Effect: additive CNS depression
- 2) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[43].

- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[43].
- 7J) Probable Mechanism: additive CNS depression

3.5.1.PJ Hydrocodone

- 1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2J) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[89]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [62].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[89]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [62].
- 7J) Probable Mechanism: additive CNS depression

3.5.1.QJ Hydromorphone

- 1J) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2J) Summary: The concomitant use of [HYDROmorphone](#) and other CNS depressants, such as antipsychotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphone](#) and an antipsychotic together, dose reduction of one or both of the medications should be considered[24].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of [HYDROmorphone](#) and other CNS depressants, such as antipsychotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[24].
- 7J) Probable Mechanism: additive CNS depression

3.5.1.RJ Kava

- 1J) Interaction Effect: additive [DOPamine](#) antagonist effects
- 2J) Summary: Theoretically, kava may add to the effect of [DOPamine](#) antagonists, increasing the risk for adverse effects. Case reports describe what appears to be DOPamine-blocking activity of kava manifested in patients as [dystonia](#), [dyskinesias](#), and [Parkinsonism](#)[19][20]. Kava extracts antagonized apomorphine-induced hyperreactivity to external stimuli in mice, suggesting [DOPamine](#) blockade activity [21].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of kava with **DOPamine** antagonists. The desired effect and/or adverse effects of the **DOPamine** antagonist may be increased or may be variable depending on the time of administration of kava and the quality of the kava product (i.e., whether it contains a standardized amount of kava).

7) Probable Mechanism: **DOPamine** antagonist effect of kava

8) Literature Reports

a) A 27-year-old Aboriginal Australian male presented three times following heavy kava use with symptoms of severe **choreoathetosis** of the limbs, trunk, neck, and facial musculature, and athetosis of the tongue. Level of consciousness was not impaired. Symptoms resolved within 12 hours of intravenous **diazepam** on each occasion. **Acute rheumatic fever** was excluded, cerebrospinal fluid and **computed tomography** of the brain was normal, and urinary drug screen was negative. The only abnormalities found in hematological and biochemical tests were a serum **alkaline phosphatase** of 162 international units/liter (IU/L) (normal: 35-135 IU/L) and serum gamma-glutamyltransferase of 426 IU/L (normal less than 60 IU/L). These were attributed to kava use. The patient did not drink alcohol [17].

b) A 76-year-old female with **idiopathic Parkinson's disease** of 17 years' duration treated for 8 years with **levodopa** 500 milligrams (mg) and benserazide 125 mg was prescribed kava extract (Kavasporal Forte(R)) 150 mg twice daily for complaints of inner tension. Within 10 days, she noted a pronounced increase in her daily "off" periods both in terms of duration and number. Within 2 days of discontinuing the kava product, symptoms had returned to her normal baseline [18].

c) A 63-year-old female experienced sudden and acute forceful involuntary oral and lingual **dyskinesias** on the fourth day of self-initiated therapy with kava extract (Kavasporal Forte(R)) 150 mg three times daily. She was treated successfully in the emergency room with **biperiden** 5 mg intravenously. She denied taking any other medications in the months preceding this event [18].

d) A 22-year-old female took kava extract (Laitan(R)) 100 mg once for anxiety and nervousness. Within four hours she experienced oral and lingual **dyskinesias**, tonic rotation of the head, and painful twisting trunk movements. She was treated successfully with **biperiden** 2.5 mg intravenously. She denied taking any other medications in the months preceding this event [18].

e) A 28-year-old male experienced acute involuntary neck extension with forceful upward deviation of the eyes within 90 minutes of taking kava extract (Laitan(R)) 100 mg. Symptoms resolved spontaneously within 40 minutes. This man had a history of acute dystonic reactions following exposure to promethacin (50 mg) and fluspirilene (1.5 mg), which had responded **biperiden** 5 mg intravenously 9 and 12 years previously [18].

3.5.1.S) **Lithium**

1) Interaction Effect: weakness, **dyskinesias**, increased extrapyramidal symptoms, **encephalopathy**, and brain damage

2) Summary: An encephalopathic syndrome followed by irreversible brain damage has occurred in a few patients treated with **lithium** plus a **DOPamine-2** antagonist, particularly **haloperidol**. A causal relationship between these events and the concomitant administration of a **DOPamine-2** antagonist and **lithium** has not been established[82]. Coadministration of **lithium** and a number of antipsychotic drugs

has caused a wide variety of encephalopathic symptoms, brain damage, extrapyramidal symptoms, and [dyskinesias](#) in isolated case reports. In most cases, these effects have occurred with therapeutic [lithium](#) levels [83][84][85]. However, many series and trials have reported using such combinations with no severe adverse consequences [86]. The mechanism is not fully understood, but chronic [lithium](#) treatment decreases neostriatal DOPaminergic activity, probably through a direct action on the G protein and the capacity of the G proteins, once activated, to stimulate adenyl cyclase [87]. Hyperglycemic reactions have also occurred during combined phenothiazine and [lithium](#) use [88].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of [DOPamine-2](#) antagonists, particularly [haloperidol](#), and [lithium](#) are used. Serum [lithium](#) levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.

7) Probable Mechanism: unknown

8) Literature Reports

a) Concomitant [haloperidol](#) and [lithium](#) therapy has resulted in symptoms of [encephalopathy](#), confusion, extrapyramidal symptoms, and fever in several patients with mania [71][72][73]. Irreversible [neurological injuries](#) have been reported [74][75].

b) Seizures, [encephalopathy](#), [delirium](#), and abnormal EEG occurred in four patients during combined [lithium](#) and [thioridazine](#) therapy [76]. Serum [lithium](#) levels were below 1 mEq/L at the time of the toxic reaction in all cases. All patients had previously tolerated [lithium](#) in combination with another phenothiazine. Three of these patients developed symptoms within eight days of initiating combination therapy.

c) The addition of [lithium](#) to [neuroleptic therapy](#) exacerbated extrapyramidal symptoms (EPS) in a small study [77]. The patients had received at least five days of treatment with either oral [thiothixene](#), [haloperidol](#), or [fluphenazine](#) in mean doses of 607.5 [chlorpromazine](#) equivalents prior to initiation of the [lithium](#) and were experiencing drug-induced extrapyramidal symptoms. Oral [lithium](#) was added when clinically indicated in sufficient doses to achieve a therapeutic serum concentration. The maximum levels attained were 0.65 to 1.27 mEq/L. The EPS ratings increased in all ten patients following the addition of [lithium](#). However, only three patients developed marked symptoms and no patient developed [lithium](#) toxicity. Significantly increased symptoms included gait, shoulder shaking, elbow rigidity, and tremor.

d) Ten patients treated with [clozapine](#) and [lithium](#) were studied [78]. Of the ten patients, four experienced significant neurologic effects, including jerking of limbs, [facial spasms](#) and tics, tremor of hands and arms, tongue twitching, and stumbling gait. One of these also experienced [delirium](#). These effects reversed when [lithium](#) was discontinued or given at a lower dose. On rechallenge, one of two patients suffered recurrence of symptoms. By keeping serum [lithium](#) no greater than 0.5 mEq/L, [clozapine](#) could be safely coadministered.

e) [Chlorpromazine](#) serum levels can be significantly reduced in the presence of [lithium](#) treatment. If used concurrently, abrupt cessation of [lithium](#) may result in rebound elevation of [chlorpromazine](#) levels, resulting in [chlorpromazine](#) toxicity. In patients on a lithium-chlorpromazine combination, abrupt withdrawal of the [lithium](#) may precipitate [chlorpromazine cardiotoxicity](#). In this report, such toxicity was manifested as sudden [ventricular fibrillation](#) associated with prolongation of the QTc interval. Hypotension and EPS are also possible in this situation [79].

f) However, other data do not support that such adverse events are frequent or indeed causally related to combination therapy. Combination of **DOPamine** antagonist antipsychotic drugs and **lithium** have been used successfully in many patients with **manic-depressive illness**. It has been proposed that the interaction may only become significant with very high doses of one or both drugs or with failure to discontinue dosing in the presence of toxic symptoms [80].

g) A 69-year-old patient with oxygen-dependent **chronic obstructive pulmonary disorder** and a 25-year history of **bipolar disorder** was started on **risperidone** 3 mg for the treatment of new-onset auditory and visual hallucinations. She had also been maintained on a regimen of **lithium** (450 mg daily) for more than 10 years. In addition, she was given **amantadine** (100 mg twice daily) for tremor. Three weeks after the start of **risperidone**, the patient experienced a decline in mental status in addition to dizziness, worsening tremors, nausea and vomiting, polyuria, depression, and visual and auditory hallucinations. She was then admitted to the hospital for **delirium**. Her **lithium** serum level was 1.36 mEq/L at the time of the admission. All medications were discontinued. Although her **lithium** level decreased to 0.41 mEq/L, she continued to experience profound **delirium**, tremors, lethargy, and hallucinations for almost one week. After she started to respond to commands, she was restarted on **lithium** (300 mg at bedtime) because of the onset of mild **hypomania**. Five days later, she was discharged with a regimen of **lithium** and low-dose **lorazepam** for treatment of insomnia. It is suggested that **delirium** could have been caused by the concurrent use of **lithium** and **risperidone**. Other factors could also have caused **delirium**, such as the patient's serum **lithium** level and the underlying **pulmonary pathology**. In addition, **amantadine**, which facilitates the release of presynaptic **DOPamine** and has a mild anticholinergic effect, may have contributed [81].

3.5.1.T] Lithospermum

- 1) Interaction Effect: decreased effectiveness of **DOPamine** antagonists
- 2) Summary: Theoretically, the **DOPamine** agonist activity of lithospermum may oppose that of **DOPamine** antagonists, decreasing their effectiveness. Lithospermum likely decreases prolactin secretion via **DOPamine** stimulation[67]. Animal data suggest that the effect occurs rapidly within 3 hours after injection, subsiding within 6 to 9 hours [68]. The magnitude and clinical significance of this phenomenon has yet to be determined in humans. Furthermore, it is not known if the ability to stimulate **DOPamine** receptors is limited to the hypothalamic region or if such an effect will be noted elsewhere (i.e., if patients with **psychosis** will experience worsening of their condition due to **DOPamine** stimulation secondary to lithospermum). Caution is recommended until the effects on humans and possible implications of a drug-herb interaction with **DOPamine** antagonists can be fully determined.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: If therapy is initiated with lithospermum and a **DOPamine** antagonist, monitor closely for return of symptoms previously controlled by the **DOPamine** antagonist.
- 7) Probable Mechanism: **DOPamine** agonism of lithospermum may counteract **DOPamine** antagonists
- 8) Literature Reports

a) Administration of freeze dried extracts (FDE) of *Lithospermum officinale* (Boraginaceae) by **intravenous injection** to rats resulted in reduced prolactin serum levels and hypophyseal stores. When administered diluent, prolactin levels decreased from 36 +/- 8 nanograms/milliliter (ng/mL) serum to 10 +/- 4 ng/mL serum (p less than 0.005) when administered *Lithospermum officinale* FDE (40 milligrams (mg)/100 grams body weight) within 3 hours post intravenous administration. The authors concluded that *Lithospermum officinale* possibly impacted prolactin secretion at the hypothalamic site via **DOPamine** stimulation [65].

b)) Prolactin levels decreased rapidly below basal values in rats within the first 3 hours following a single [intravenous injection](#) of *Lithospermum officinale*. Prolactin levels returned to control levels within 6 to 9 hours after the injection [66].

3.5.1.U] [Meperidine](#)

1)) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2)) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

7)) Probable Mechanism: additive CNS depression

3.5.1.V] [Methadone](#)

1)) Interaction Effect: increased risk of CNS depression

2)) Summary: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[28].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[28].

7)) Probable Mechanism: additive CNS depression effects

3.5.1.W] [Metoclopramide](#)

1)) Interaction Effect: an increased risk of extrapyramidal reactions or [neuroleptic malignant syndrome](#)

2)) Summary: Concomitant use of [metoclopramide](#) with antipsychotic agents may increase the risk of extrapyramidal symptoms, such as [tardive dyskinesia](#) or [neuroleptic malignant syndrome](#), and is contraindicated[22]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions.

Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [23].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [metoclopramide](#) with antipsychotic agents is contraindicated[22]. If concurrent therapy is required, monitor patients for signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#) (fever, sweating, confusion, muscle stiffness). Discontinue [metoclopramide](#) if patient develops signs and symptoms of extrapyramidal reactions or [neuroleptic malignant syndrome](#). Injection of [diphenhydramine](#) 50 mg intramuscularly or [benztropine](#) 1 to 2 mg intramuscularly may reverse the extrapyramidal reactions [23].

7) Probable Mechanism: unknown

3.5.1.X] Milnacipran

1) Interaction Effect: increased risk of [serotonin syndrome](#) ([hypertension](#), [hyperthermia](#), myoclonus, mental status changes)

2) Summary: Concomitant use of milnacipran and an antipsychotic may result in [hypertension](#), coronary artery vasoconstriction or [serotonin syndrome](#), which may be life-threatening. When concomitant use of milnacipran and an antipsychotic is required, caution should be used. If symptoms of [serotonin syndrome](#) develop (eg, restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, overreactive reflexes, nausea, vomiting, and diarrhea), treatment should be immediately discontinued and the appropriate supportive therapy initiated[42].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of milnacipran and an antipsychotic may result in [hypertension](#) and coronary artery vasoconstriction through additive serotonergic effects. Therefore, use caution when coadministering these agents. If symptoms of [serotonin syndrome](#) develop, discontinue treatment immediately and institute the appropriate supportive symptomatic treatment[42].

7) Probable Mechanism: additive serotonergic effect

3.5.1.Y] Morphine

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[39][40][41].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[39][40][41].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.ZJ Morphine Sulfate Liposome

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant [morphine](#) and other CNS depressants for hypotension, [respiratory depression](#) and sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[39][40][41].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [morphine](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, [respiratory depression](#) or sedation, initiate [morphine](#) at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[39][40][41].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.AA Oxycodone

1J) Interaction Effect: increased risk of CNS depression

2J) Summary: Use caution with concomitant use of the CNS depressant [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[32]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [33][34].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Use caution with concomitant use of [oxycodone](#) with another CNS depressant, as additive CNS depressant effects, such as [respiratory depression](#), hypotension, and profound sedation, can progress to coma or death. Assess the duration of use and degree of tolerance to CNS depressants (including alcohol and illicit drugs) before concurrent use. If coadministration is clinically necessary, monitor the patient and decrease the dose of 1 or both drugs[32]. Initiate [oxycodone](#) controlled-release formulations at one-third to one-half of the usual dosage [33][34].

7J) Probable Mechanism: additive CNS depression effects

3.5.1.AB Oxymorphone

1J) Interaction Effect: increased risk of [respiratory depression](#), profound sedation, coma, and death

2J) Summary: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects and an increased risk of [respiratory depression](#), profound sedation, coma, and death. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation, hypotension, and [respiratory depression](#), and consider reducing the CNS depressant dose[35].

3J) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [oxymorphone](#) and a CNS depressant may result in additive respiratory and CNS depressant effects. If concurrent use is clinically necessary, initiate [oxymorphone](#) at a dose of 5 mg every 12 hours. Monitor patients for sedation and [respiratory depression](#), sedation, and hypotension, and consider reducing the CNS depressant dose[35].
- 7) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.AC] [Pentazocine](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [pentazocine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [pentazocine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AD] [Periciazine](#)

- 1) Interaction Effect: risk of enhanced CNS depression
- 2) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[26][27].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[26][27].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AE] [Phenylalanine](#)

- 1) Interaction Effect: increased incidence of [tardive dyskinesia](#)
- 2) Summary: Taking [phenylalanine](#) concomitantly with certain neuroleptic drugs may exacerbate [tardive dyskinesia](#)[61]. Abnormal [phenylalanine](#) metabolism in certain patients may lead to [phenylalanine](#) accumulation in the brain and in turn, reduced brain availability of other large neutral amino acids. This may interfere with the synthesis of catecholamines [61].
- 3) Severity: moderate
- 4) Onset: rapid

5J) Substantiation: theoretical

6J) Clinical Management: Caution is advised if [phenylalanine](#) is administered with a neuroleptic agent. Monitor the patient closely for signs of [tardive dyskinesia](#).

7J) Probable Mechanism: reduced brain availability of other large neutral amino acids and interference with catecholamine synthesis

8J) Literature Reports

aJ) [Phenylalanine](#) tended to increase the incidence of [tardive dyskinesia](#) in patients taking neuroleptics in an open study. Three groups of patients were studied: (1) patients with [unipolar depression](#) with [tardive dyskinesia](#) (n=11), (2) patients with no [tardive dyskinesia](#) with current or past exposure to greater than or equal to 100 milligrams (mg) of a [chlorpromazine](#) equivalent for at least 3 months (n=10), and (3) patients with no [tardive dyskinesia](#) not previously exposed to a neuroleptic drug (n=10). Neuroleptic agents were taken during the study by 6 patients in group 1, and 5 patients in group 2. Patients received powdered [phenylalanine](#) 100 mg/kilogram dissolved in orange juice after an overnight fast. Blood samples were obtained just prior to [phenylalanine](#) administration and 2 hours after administration. Three patients in group 1 (with [tardive dyskinesia](#)) had the highest postloading [phenylalanine](#) plasma levels, this group as a whole had higher (though nonsignificant) mean [phenylalanine](#) levels than the other groups. [Tardive dyskinesia](#) score (measured using the [Abnormal Involuntary Movements Scale \(AIMS\)](#)) nonsignificantly increased in group 1. Postloading [phenylalanine](#) level and postloading AIMS scores were significantly positively correlated in group 1 (rs=0.347, p less than 0.05; Spearman correlation coefficient 0.543, p less than 0.05). Postloading [phenylalanine](#) level and baseline AIMS scores demonstrated a trend toward correlation (rs=0.246, p=0.092; Spearman correlation coefficient 0.679, p less than 0.05). In all patients, [phenylalanine](#) loading increased plasma [phenylalanine](#) levels approximately eight-fold, and plasma tyrosine increased 2.5 times as a result of conversion of [phenylalanine](#) to tyrosine. Plasma levels of competing large neutral amino acids such as tryptophan decreased slightly [60].

3.5.1.AF] [Remifentanil](#)

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2J) Summary: The concomitant use of [remifentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of [remifentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].

7J) Probable Mechanism: additive CNS depression

3.5.1.AG] [Sufentanil](#)

1J) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

- 2J) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[62].
- 7J) Probable Mechanism: additive CNS depression

3.5.1.AHJ Tapentadol

- 1J) Interaction Effect: increased risk of CNS depression
- 2J) Summary: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[29].
- 3J) Severity: major
- 4J) Onset: unspecified
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Concomitant use of tapentadol, which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patient's degree of tolerance to CNS depressants. If tapentadol is coadministered with a CNS depressant, initiate the dose of tapentadol ER at 50 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[29].
- 7J) Probable Mechanism: additive CNS depression effects

3.5.1.AIJ Tramadol

- 1J) Interaction Effect: an increased risk of seizures
- 2J) Summary: Seizures have been reported in patients using [tramadol](#). The manufacturer of [tramadol](#) states that combining neuroleptic medications with [tramadol](#) may enhance the risk of seizures[36].
- 3J) Severity: major
- 4J) Onset: rapid
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Caution should be used if [tramadol](#) is to be administered to patients receiving [neuroleptic therapy](#). If possible, avoid this combination, especially in patients with underlying conditions that might predispose to seizures.
- 7J) Probable Mechanism: unknown

3.5.1.AJ Vitex

- 1J) Interaction Effect: decreased effectiveness of [DOPamine](#) antagonists

- 2) Summary: Theoretically, the **DOPamine** agonist activity of Vitex may oppose that of **DOPamine** antagonists, decreasing their effectiveness. Vitex has been effective in alleviating **luteal phase defects** due to **hyperprolactinemia** and in relieving symptoms related to **premenstrual tension syndrome**[57][58]. Vitex reduced prolactin secretion in humans [57]. In vitro, Vitex inhibited prolactin release by binding to the D2 receptor [59].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: established
- 6) Clinical Management: If therapy is initiated with Vitex and a **DOPamine** antagonist, monitor closely for return of symptoms previously controlled by the **DOPamine** antagonist.
- 7) Probable Mechanism: **DOPamine** agonism of Vitex may counteract **DOPamine** antagonists
- 8) Literature Reports

a) Vitex agnus castus (Vitex) effectively normalized prolactin release in a randomized double-blind, placebo-controlled trial of 52 women with **luteal phase defects** due to latent **hyperprolactinemia**. Administration of Vitex agnus castus 20 mg daily for three months reduced prolactin release (from 23.7 to 22.5 nanogram (ng)/mL; p equal to 0.23), normalized shortened luteal phases (from 5.5 days to 10.5 days; p less than 0.005), and eliminated deficits in luteal **progesterone** synthesis (from 2.46 ng/mL to 9.69 ng/mL; p less than 0.001). No side effects were noted [54].

b) Vitex agnus castus and **pyridoxine** caused a similar reduction on the **premenstrual tension** scale (PMTS) in a randomized, controlled trial of 127 women with PMTS. Patients taking Vitex agnus castus (Agnolyt(R)) experienced more relief from breast tenderness, inner tension, headache, edema, constipation, and depression than those taking **pyridoxine**. Patients in the Vitex agnus castus group receive one capsule of Agnolyt(R) and one placebo capsule daily for 3 menstrual cycles. Patients in the **pyridoxine** group received one placebo capsule twice daily on days 1-15 of the menstrual cycle and **pyridoxine** 100 mg twice daily on days 16 to 35 of the menstrual cycle for 3 menstrual cycles. Unspecified gastrointestinal disturbances occurred in the treatment group along with two cases of skin reaction and one transient headache [55].

c) In vitro, Vitex (Agnus castus) was found to bind to the D2 receptor in rat pituitary cell cultures. Basal prolactin release was significantly inhibited by 0.5 milligram (mg) and 1 mg of vitex extract/mL culture medium (p less than 0.05). Agnus castus extract doses from 0.125 mg/mL to 1 mg/mL significantly suppressed prolactin release in cells stimulated by thyrothrin releasing hormone (TRH) (p less than 0.05). DOPaminergic action was demonstrated in the rat corpus striatum membrane **DOPamine** receptor assay. Agnus castus extract did not affect basal **luteinizing hormone** (LH) or **follicle-stimulating hormone** (FSH), indicating selectivity for prolactin secretion, and not generalized inhibition of pituitary hormone secretion. The effect was not due to a cytotoxic effect as demonstrated by the lack of effect on the MTT-conversion test. The authors concluded that Agnus castus exerted its prolactin inhibiting effect via stimulation of D2 receptors in the pituitary [56].

3.5.1.AK] Zotepine

- 1) Interaction Effect: increased risk of seizures
- 2) Summary: Zotepine used concurrently with neuroleptics may increase the risk of seizures[52][53].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: theoretical

6)) Clinical Management: Monitoring for seizures is particularly important in those patients who: (1) are taking large doses of zotepine; (2) have a history of seizure disorders; (3) are of young age; or (4) have a past history of [brain injury](#).

7)) Probable Mechanism: unknown

4.0] Clinical Applications

[Monitoring Parameters](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1] Monitoring Parameters

A)) [Molindone](#) Hydrochloride

1)) Therapeutic

a)) Improvement of the clinical signs and symptoms of the condition being treated, eg, schizophrenic behavior/affect.

2)) Toxic

a)) Anticholinergic side effects, eg, blurred vision, dry mouth, constipation.

b)) [Complete blood counts](#)

c)) Liver function tests

d)) [Renal function tests](#)

4.3] Place In Therapy

A)) Current users of atypical antipsychotic drugs and typical antipsychotic drugs (including [molindone](#)) had a similar dose-dependent risk of sudden cardiac death, according to a retrospective cohort of 93,300 adult users of antipsychotic drugs and 186,600 matched controls. The study included patients age 30 to 74 years (mean 45.7 +/- 11.8 years) with similar cardiovascular risk at baseline who had at least one filled prescription and had 1 outpatient visit in each of the 2 preceding years. Sudden cardiac death was defined as occurring in the community and excluded deaths of patients admitted to the hospital, non-sudden deaths, deaths due to extrinsic causes, or causes not related to ventricular [tachyarrhythmia](#). Current use was defined as the interval between the time the prescription was filled and the end of the day's supply. Low and high doses was defined as comparable to less than 100 milligrams (mg) of [chlorpromazine](#), and doses comparable to [chlorpromazine](#) 300 mg or greater, respectively. The adjusted rate of sudden cardiac death (incidence-rate ratio) in current users of atypical antipsychotic drugs in 79,589 person-years was 2.26 (95% CI, 1.88 to 2.72, p less than 0.001) which was similar to the risk in current users of typical antipsychotic drugs in 86,735 person-years which was 1.99 (95% CI, 1.68 to 2.34, p less than 0.001). The risk of sudden cardiac death significantly increased with increasing dose in both the typical and atypical antipsychotic drug groups. In typical antipsychotic use, the incidence rate ratio increased from 1.31 (95% CI, 0.97 to 1.77) in low-dose use to 2.42 (95% CI, 1.91 to 3.06) in high-dose use. To limit the effects of confounding of the study results, there was a secondary analysis performed in a cohort of patients matched by propensity score, which resulted in a similar risk of sudden death as the primary cohort analysis [101]. In an editorial in The New England Journal of Medicine, it has been

suggested that antipsychotic drugs continue to be used in patients with clear evidence of benefit, but in vulnerable populations with cardiac risk profiles (eg, elderly patients), there should be an age-dependent justification required prior to administration. It has also been suggested (although not formally tested) that ECGs be performed before and shortly after initiation of antipsychotic therapy to screen for existing or emergent QT interval prolongation [102].

B) [Molindone](#) is an oxygenated indole compound with antipsychotic activity and is structurally different from the phenothiazines, thioxanthenes, and butyrophenones. It is a potent neuroleptic and is associated with a high incidence of extrapyramidal symptoms but has a low incidence of sedation, anticholinergic effects, and cardiovascular effects [103].

C) Clinical evidence demonstrates that all of the commonly marketed neuroleptic agents have therapeutic equivalence when adequate doses are utilized [104]. When a flexible dosage regimen is used to titrate the chosen agent to maximum effect, all neuroleptics will demonstrate statistical equivalence in a study population. However, one agent may be effective while another will not. Pharmacokinetic and pharmacodynamic differences as well as possible multiple etiologies of the patient's [schizophrenia](#) may be reasons for the individual variance [103]. The patient's past medication history of neuroleptic agents should play an important role in drug selection. The patient's subjective response to neuroleptics should also be used in deciding on a specific agent. A reduction in symptoms or a pleasurable response following the first neuroleptic dose will improve patient compliance better than if the patient has a bad experience after the first dose [105]. The last factor in deciding which neuroleptic agent to use is its adverse effect profile. Almost all neuroleptic agents possess similar adverse effects; however, the overall incidence of a particular category of adverse effects varies between the agents.

D) [Molindone](#) is effective in treating acute and chronic cases of [schizophrenia](#) [9][106]. However, it does not appear to have any advantages over other neuroleptic agents, but may be effective in some patients who are unresponsive to them. The addition of [molindone](#) to the formulary should be based on the particular institution's clinical experience with the drug.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) [Molindone](#) is an oxygenated indole derivative of the dihydroindolone compounds differing structurally from other antipsychotic drugs such as the phenothiazines, thioxanthenes, and butyrophenones. [Molindone](#) chemically is 3-ethyl-6,7-dihydro-2-methyl-5-morpholinomethyl-4-(5H)-one hydrochloride. It is a white, slightly basic, crystalline powder, freely soluble in water and alcohol and has a molecular weight of 312.67.

2) Other oxygenated indole compounds with psychopharmacological effects are the naturally occurring serotonin, bufotenine, and psilocin and [reserpine](#) and oxypertine. [Molindone](#), however, exhibits marked differences from [reserpine](#) and oxypertine structurally and pharmacologically, their indole containing structure being their common relationship [94].

3) Effects from [molindone](#) are a result of its action on the ascending reticular activating system. The activity of [molindone](#) has been shown to be similar to that of the major tranquilizers, eg, phenothiazines, etc. In animals, spontaneous activity and reactivity to sensory stimuli is decreased. Arousal is blunted, aggressiveness is diminished, and conditioned avoidance response is blocked in normal doses. [Molindone](#) also blocks the increase in blood pressure following [epinephrine injection](#). Potential antidepressant properties are suggested by its potentiation of 5-hydroxytryptophan and its antagonism of tetrabenazine induced-ptosis. It has been suggested, however, that in humans, the mood elevating effect of [molindone](#) as well as other psychotherapeutic agents is an indirect result of their antipsychotic effects. The antiemetic and analgesic action of [molindone](#) has also been demonstrated in animals [94]; (Sugerman & Hermann, 1967) [97][98].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Molindone Hydrochloride

4.5.1.A.1] Schizophrenia

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years or older)

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

b) Summary:

Evidence

Efficacy was established in newly and chronically hospitalized, acutely ill, schizophrenic patients [2].

Several clinical trials have documented the efficacy of [molindone](#) in acute and chronic types of [schizophrenia](#) (Kellner et al, 1976; Gallant et al, 1973; Abuzzahab, 1973b).

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Chlordiazepoxide

4.6.A.1] Neurosis

a) Two studies comparing [chlordiazepoxide](#) with [molindone](#) in the treatment of [psychoneuroses](#) and [anxiety neuroses](#) revealed that both agents were superior to placebo but that no significant difference was observed between the 2 agents [118][119]. There is some evidence that [chlordiazepoxide](#) is significantly more effective in reducing insomnia in these patients [118].

4.6.B] Chlorpromazine

4.6.B.1] Chronic schizophrenia

a) In a double-blind, placebo-controlled, randomized study of 44 patients with [chronic schizophrenia](#), the antipsychotic effects of [molindone](#) 20 to 100 milligrams/day (average 90 mg) were compared with [chlorpromazine](#) 200 to 1000 milligrams/day (average 892 mg) [107]. [Chlorpromazine](#) produced over all superiority in the study displaying statistically significant improvement in more aspects compared with [molindone](#) as rated by the Brief Psychiatric Rating Scale (BPRS) and Nurse's Observation Scale for Inpatient Evaluation (NOSIE) scales. [Molindone](#), however, produced significantly more improvement (CPZ not showing significant improvement) in the aspects of hostility (BPRS p less than 0.05) compared with placebo, social interest factor (NOSIE p less than 0.05), and the finger tapping test from the psychometric battery (p less than 0.05), possibly suggesting a more alerting effect with [molindone](#). Extrapyramidal signs were noted with [molindone](#) only. The absence of these signs in the [chlorpromazine](#)

group could not be explained. Molindone had no significant effect on serum cholesterol (no statistical analyses made). Hypotension, drowsiness, and weight gain were seen more often with chlorpromazine. Lactation was seen with equal frequency in all groups including placebo.

4.6.C] Haloperidol

4.6.C.1] Psychotic disorder

a) Molindone and haloperidol were comparable in a study of 24 acutely psychotic patients [109]. The dose of molindone was 25 milligrams 2 to 4 times/day (+ as needed) the dose of haloperidol was 5 milligrams 2 to 4 times/day (+ as needed). Both drugs were given intramuscularly. Evaluation of results was based on Brief Psychiatric Rating Scale, Target Symptom Rating Scale, and Clinical Global Impression.

b) Molindone (up to 225 milligrams/day by injection followed by up to 500 mg/day orally) was compared with haloperidol (up to 45 milligrams/day by injection followed by 100 mg/day orally) in 35 acutely schizophrenic patients in a double-blind study. There were no significant differences in efficacy or safety over the 4 weeks of the study [110].

4.6.C.2] Tardive dyskinesia

a) Haloperidol was more effective than molindone at masking tardive dyskinesia which was exacerbated by withdrawal of neuroleptic medication. Molindone was compared with haloperidol with regard to their ability to mask neuroleptic withdrawal-exacerbated tardive dyskinesia, using the theoretical proposition that agents less able to mask are less dyskinetogenic [111]. In a parallel, double-blind study, 11 patients were given either molindone or haloperidol in doses ranging from 50% to 200% dose equivalency to the neuroleptics from which they had been removed, at a point after discontinuation where involuntary movements showed a significant increase. At doses that were equivalent to 200% of the prestudy neuroleptic dose, molindone was shown to be less able to mask neuroleptic withdrawal-exacerbated tardive dyskinesia than was haloperidol, thereby suggesting lower dyskinetogenic potential.

4.6.D] Thioridazine

4.6.D.1] Disruptive behavior disorder

a) Molindone and thioridazine were equally efficacious in an 8-week, double-blind, placebo-controlled, parallel design study that compared molindone (n=15) with thioridazine (n=16) in 31 aggressive male children with conduct disorder [108]. Both drugs resulted in significant improvement in Aggression Scale score and CPRS evaluation of hostility and antisocial and violent behavior when compared to the placebo periods before and after the 4-week treatment cycle. The overall mean molindone dose was 1.3 milligrams/kilogram/day and the thioridazine mean dose was 4.64 milligrams/kilogram/day.

4.6.E] Tranylcypromine

4.6.E.1] Depression, Refractory

a) Molindone was found to be more effective and less toxic than tranylcypromine in a single-blind, parallel study of 20 hospitalized patients with refractory depression [120]. Patients received either molindone 10 to 30 milligrams/day or tranylcypromine 20 to 30 milligrams/day. Patients treated with molindone showed a positive response within the first week, especially in the areas of anxiety and agitation. Although extrapyramidal symptoms developed in 50% of the patients taking molindone, these were effectively managed with amantadine. Seven patients receiving tranylcypromine withdrew from the study due to clinical worsening and/or side effects. None of the patients receiving the molindone withdrew from the study. Molindone appears to be superior to tranylcypromine in the management of refractory depression.

4.6.F] Trifluoperazine

4.6.F.1] Schizophrenia

a) Several controlled clinical studies have found that the therapeutic effectiveness of **molindone** in acute and **chronic schizophrenia** is similar to that of **trifluoperazine** [112][113][114][115][116].

b) **Molindone** and **trifluoperazine** were equally efficacious in a double blind, randomized study [117]. **Molindone** was compared with **trifluoperazine** in 24 chronic schizophrenic patients to determine its therapeutic dose range, its euphoric and antidepressant properties, its antipsychotic effects, and comparative efficacy. Effects of the drugs were by means of the Brief Psychiatric Rating Scale (BPRS) and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE), an observation of ward behavior, and independent global ratings of improvement by two psychiatrists. Both drugs were given in doses of 10 milligrams/day increasing to a maximum of 80 mg/day. All patients were receiving daily doses of 40 mg/day by the end of 4 weeks. **Trifluoperazine** showed somewhat greater efficacy than **molindone** but this was not statistically significant. Both drugs produced significant improvement in social competence, neatness, irritability, and manifest **psychosis** (p less than 0.01) rated by the NOSIE scale. The BPRS showed a statistical improvement with both drugs only in the aspect of unusual thought content. NOSIE scale ratings indicated that 2/3 of the patients in the **trifluoperazine** group were rated as improved as opposed to 1/3 in the **molindone** group. This, however, was proven nonsignificant on chi-square analysis. The investigators felt, however, that the dosage of **molindone** was not at its optimal therapeutic level for severely ill patients.

c) In a placebo-controlled study comparing **molindone** to **trifluoperazine** in 40 patients, the placebo group showed significant improvement on the NOSIE Social Competence (p less than 0.001), NOSIE Total Score (p less than 0.005), and BPRS (Brief Psychiatric Rating Scale) Total Score (p less than 0.05) [116]. This gives some indication of the difficulty in assessing the efficacy of psychotherapeutic drugs.

d) **Trifluoperazine** and **molindone** were comparable in a study of 40 patients on a 2:1 dose schedule basis [113]. Both drugs produced statistically significant improvement in the test scores (values ranged from p less than 0.05 to 0.01) with **molindone** affecting more items significantly than **trifluoperazine**, but the total effects between the two drugs did not differ significantly. Both treatment groups showed a tendency toward **relapse** upon discontinuation of the drug as shown by an increase in test scores. The **molindone**-treated group showed a greater tendency toward **relapse** than did the **trifluoperazine** group with the value rising to 88% and 73% of the control level, respectively. Side effects were noted more with **molindone** than **trifluoperazine**; however, the differences were not statistically significant.

e) **Trifluoperazine** was more effective than **molindone** in a double-blind study on a 2:1 dose basis in 37 patients [114]. The mean doses were **molindone** 75 mg and **trifluoperazine** 35 mg. The results showed that **trifluoperazine** produced a significantly greater improvement in total Brief Psychiatric Rating Scale (BPRS) ratings (P less than 0.05) improvement in 13 variables compared with significant improvement of 10 variables with **molindone** at 2 weeks. In the NOSIE ratings, this was more apparent in that there were no significant changes or trends toward improvement in the **molindone** group after 2 weeks. After 4 weeks, the BPRS scores showed that these differences had disappeared. These differences suggested that either **trifluoperazine** acts more quickly than **molindone**, that **molindone** was not administered in sufficient doses, or that **molindone** is rapidly metabolized and excreted and, therefore, the interval between doses should be reduced. Extrapyramidal symptoms, especially rigidity, occurred more frequently and with more severity in the **trifluoperazine** group.

6.0] References

- 1 American Geriatrics Society 2015 Beers Criteria Update Expert Panel : American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015; 63(11):2227-2246.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 2 Product Information: molindone HCl oral tablets, molindone HCl oral tablets. CorePharma, LLC (per DailyMed), Middlesex, NJ, 2014.
- 3 Geibig CB & Marks LW: Treatment of clozapine- and molindone-induced agranulocytosis with granulocyte colony-stimulating factor. *Ann Pharmacother* 1993; 27:1190-1192.
- 4 Katz SE: Tardive dyskinesia associated with molindone treatment. *Am J Psychiatry* 1990; 147:124-125.
- 5 Ananth J & Carrillo R: Tardive dyskinesia with molindone. *J Clin Psychiatry* 1983; 44:276.
- 6 Gradon JP: Neuroleptic malignant syndrome possibly caused by molindone hydrochloride. *DICP* 1991; 25:1071-1072.
- 7 Bernstein R: Malignant neuroleptic syndrome-an atypical case. *Psychosomatics* 1979; 20:840-846.
- 8 Johnson SB, Alvarez WA, & Freinhar JP: A case of massive rhabdomyolysis following molindone administration. *J Clin Psychiatry* 1986; 47:607-608.
- 9 Kellner R, Rada RT, Egelman A, et al: Long term study of molindone HCl in chronic schizophrenics. *Curr Ther Res* 1976; 20:686.
- 10 Kahn JL: More on galactorrhea associated with molindone. *Am J Psychiatry* 1979; 136:1617-1618.
- 11 Bhatia SC, Banta LE, & Ehrlich DW: Molindone and hepatotoxicity. *Drug Intell Clin Pharm* 1985; 19:744-746.
- 12 Kinon BJ, Liu-Seifert H, Stauffer VL, et al: Bone loss associated with hyperprolactinemia in patients with schizophrenia. *Clin Schizophr Relat Psychoses* 2013; 7(3):115-123. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 13 Krumholz WV, Sheppard C, & Merlis S: Menstruation changes as unusual side effect in molindone trial. *Curr Ther Res* 1970; 12:94.
- 14 Gill SS, Bronskill SE, Normand SL, et al: Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; 146(11):775-786. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 15 Schneeweiss S, Setoguchi S, Brookhart A, et al: Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ* 2007; 176(5):627-632. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 16 Wang PS, Schneeweiss S, Avorn J, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353:2335-2341.
- 17 Spillane PK, Fisher DA, & Currie BJ: Neurological manifestations of kava intoxication. *Med J Australia* 1997; 167(3):172-173.
- 18 Schelosky L, Raffauf C, Jendroska K, et al: Kava and dopamine antagonism. *J Neurol Neurosurg Psych* 1995; 58(5):639-640.
- 19 Spillane PK, Fisher DA, & Currie BJ: Neurological manifestations of kava intoxication. *Med J Australia* 1997; 167(3):172-173.
- 20 Schelosky L, Raffauf C, Jendroska K, et al: Kava and dopamine antagonism. *J Neurol Neurosurg Psych* 1995; 58(5):639-640.
- 21 Jamieson DD, Duffield PH, Cheng D, et al: Comparison of the central nervous system activity of the aqueous and lipid extract of kava (*Piper methysticum*). *Arch Int Pharmacodyn Ther* 1989; 301:66-80.
- 22 Product Information: REGLAN(R) oral tablets, metoclopramide oral tablets. Alaven Pharmaceutical LLC, Marietta, GA, 2009.
- 23 Product Information: METOZOLV ODT orally disintegrating tablets, metoclopramide hydrochloride orally disintegrating tablets. Salix Pharmaceuticals, Inc., Morrisville, NC, 2009.

- 24 Product Information: EXALGO(R) extended release oral tablets, hydromorphone hydrochloride extended release oral tablets. ALZA Corporation, Vacaville, CA, 2010.
- 25 Product Information: DIGESAN(R) oral capsules, bromopride oral capsules. Sanofi-Aventis Farmaceutica Ltda (per Anvisa), Suzano, Brazil, 2014.
- 26 Product Information: Pericyazine oral tablets, pericyzaine oral tablets. Winthrop Pharmaceuticals UK Ltd (per emc+), Guildford, Surrey, United Kingdom, 2015.
- 27 Product Information: NEULEPTIL oral capsules, drops, periciazine oral capsules, drops. ERFA Canada Inc. (per Health Canada), Montreal, QC, Canada, 2012.
- 28 Product Information: DOLOPHINE(R) oral tablets, methadone HCl oral tablets. Roxane Laboratories, Inc. (per FDA), Columbus, OH, 2014.
- 29 Product Information: NUCYNTA(R) ER oral extended-release tablets, tapentadol oral extended-release tablets. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2014.
- 30 Product Information: BELBUCA(TM) buccal film, buprenorphine buccal film. Endo Pharmaceuticals Inc. (per manufacturer), Malvern, PA, 2015.
- 31 Product Information: BUNAVAIL(TM) buccal film, buprenorphine naloxone buccal film. BioDelivery Sciences International (per FDA), Raleigh, North Carolina, 2014.
- 32 Product Information: TROXYCA(R) ER oral extended-release capsules, oxycodone HCl naltrexone HCl oral extended-release capsules. Pfizer Inc (per FDA), New York, NY, 2016.
- 33 Product Information: XTAMPZA(TM) ER oral extended-release capsules, oxycodone oral extended-release capsules. Collegium Pharmaceutical Inc (per manufacturer), Canton, MA, 2016.
- 34 Product Information: OXYCONTIN(R) oral extended release tablets, oxycodone HCl oral extended release tablets. Purdue Pharma L.P. (per FDA), Stamford, CT, 2014.
- 35 Product Information: OPANA(R) ER oral extended release tablets, oxymorphone HCl oral extended release tablets. Endo Pharmaceuticals Inc. (per FDA), Malvern, PA, 2014.
- 36 Product Information: Ultram(R), tramadol hydrochloride. Ortho-McNeil Pharmaceutical, Raritan, NJ, 1998.
- 37 Product Information: BONJESTA(R) oral extended-release tablets, doxylamine succinate pyridoxine HCl oral extended-release tablets. Duchesnay USA, Inc (per FDA), Bryn Mawr, PA, 2016.
- 38 Product Information: DICLEGIS(R) oral delayed-release tablets, doxylamine succinate pyridoxine HCl oral delayed-release tablets. Duchesnay Inc. (per manufacturer), Bryn Mawr, PA, 2013.
- 39 Product Information: KADIAN(R) oral extended-release capsules, morphine sulfate oral extended-release capsules. Actavis Pharma, Inc. (per FDA), Parsippany, NJ, 2014.
- 40 Product Information: AVINZA(R) oral extended release capsules, morphine sulfate oral extended release capsules. Pfizer Inc (per FDA), New York, NY, 2014.
- 41 Product Information: MS CONTIN(R) oral extended release tablets, morphine sulfate oral extended release tablets. Purdue Pharma L.P. (per FDA), Stamford, CT, 2014.
- 42 Product Information: SAVELLA(R) oral tablets, milnacipran hydrochloride oral tablets. Forest Pharmaceuticals, Inc, New York, NY, 2010.
- 43 Product Information: ADDYI oral tablets, flibanserin oral tablets. Sprout Pharmaceuticals, Inc. (per FDA), Raleigh, NC, 2015.

- 44 Product Information: Inapsine(R), droperidol. Akorn, Inc., Decatur, IL, 2001.
- 45 Product Information: APO-BROMAZEPAM oral tablets, bromazepam oral tablets. Apotex, Inc (per Health Canada), Weston, ON, 2013.
- 46 Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. *Movement Disord* 1989; 4(4):330-333.
- 47 Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. *Neurology* 1978; 28:1061-1064.
- 48 Abramson LB, Brown AJ, & Sitaram N: A cardioacceleratory response to low-dose arecoline infusion during sleep in patients with major depressive disorder: relationship to REM sleep induction. *Psych Res* 1985; 16:189-198.
- 49 Chu NS: Sympathetic response to betel chewing. *J Psychoact Drugs* 1995; 27(2):183-186.
- 50 Deahl M: Betel nut-induced extrapyramidal syndrome: an unusual drug interaction. *Movement Disord* 1989; 4(4):330-333.
- 51 Nutt JG, Rosin A, & Chase TN: Treatment of Huntington disease with a cholinergic agonist. *Neurology* 1978; 28:1061-1064.
- 52 Product Information: Nipolept(R), zotepine. Klinge Pharma GmbH, Munich, Germany, 1994.
- 53 Hori M, Suzuki T, Sasaki M, et al: Convulsive seizures in schizophrenic patients induced by zotepine administration. *Jpn J Psychiatry Neurol* 1992; 46:161-167.
- 54 Milewicz A, Gejdel E, Sworen H, et al: Vitex agnus castus extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study (Article in German). *Arzneimittelforschung* 1993; 43(7):752-756.
- 55 Lauritzen C, Reuter HD, Repges R, et al: Treatment of premenstrual tension syndrome with Vitex agnus castus: controlled, double-blind study versus pyridoxine. *Phytomedicine* 1997; 4:183-189.
- 56 Jarry H, Leonhardt S, Gorkow C, et al: In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of *Agnus castus*: direct evidence for a dopaminergic principle by the dopamine receptor assay. *Exp Clin Endocrinol* 1994; 102:448-454.
- 57 Milewicz A, Gejdel E, Sworen H, et al: Vitex agnus castus extract in the treatment of luteal phase defects due to latent hyperprolactinemia. Results of a randomized placebo-controlled double-blind study (Article in German). *Arzneimittelforschung* 1993; 43(7):752-756.
- 58 Lauritzen C, Reuter HD, Repges R, et al: Treatment of premenstrual tension syndrome with Vitex agnus castus: controlled, double-blind study versus pyridoxine. *Phytomedicine* 1997; 4:183-189.
- 59 Jarry H, Leonhardt S, Gorkow C, et al: In vitro prolactin but not LH and FSH release is inhibited by compounds in extracts of *Agnus castus*: direct evidence for a dopaminergic principle by the dopamine receptor assay. *Exp Clin Endocrinol* 1994; 102:448-454.
- 60 Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar depressed patients with and without tardive dyskinesia. *Neuropsychopharmacology* 1992; 6(4):241-247.
- 61 Gardos G, Cole JO, Matthews JD, et al: The acute effects of a loading dose of phenylalanine in unipolar depressed patients with and without tardive dyskinesia. *Neuropsychopharmacology* 1992; 6(4):241-247.
- 62 US Food and Drug Administration (FDA): Drug Safety Communications: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. US Food and Drug Administration (FDA). Silver Spring, MD. 2016. Available from URL: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM518672.pdf>. As accessed 2016-08-31.
- 63 Howard JE: Severe psychosis and the adrenal androgens. *Integr Physiol Behav Sci* 1992; 27:209-215.

- 64 Howard JE: Severe psychosis and the adrenal androgens. *Integr Physiol Behav Sci* 1992; 27:209-215.
- 65 Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts. TSH- and prolactin-suppressing properties of *Lithospermum officinale* and other plants. *Planta Medica* 1982; 45(2):78-86.
- 66 Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts on hypophyseal hormones in the rat. *Acta Endocrinol* 1980; 234(Suppl):49.
- 67 Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts. TSH- and prolactin-suppressing properties of *Lithospermum officinale* and other plants. *Planta Medica* 1982; 45(2):78-86.
- 68 Sourgens H, Winterhoff H, Gumbinger HG, et al: Antihormonal effects of plant extracts on hypophyseal hormones in the rat. *Acta Endocrinol* 1980; 234(Suppl):49.
- 69 Product Information: DURAGESIC(R) transdermal system, fentanyl transdermal system. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2012.
- 70 Product Information: Versed(R), midazolam HCl injection. Roche Pharmaceuticals, Nutley, NJ, 2000.
- 71 Cohen WJ & Cohen NH: Lithium carbonate, haloperidol and irreversible brain damage. *JAMA* 1974; 230:1283-1287.
- 72 Loudon JB & Waring H: Toxic reactions to lithium and haloperidol (letter). *Lancet* 1976; 2:1088.
- 73 Thomas CJ: Brain damage with lithium/haloperidol (letter). *Br J Psychiatry* 1979; 134:552.
- 74 Sandyk R & Hurwitz MD: Toxic irreversible encephalopathy induced by lithium carbonate and haloperidol. *S Afr Med J* 1983; 65:875-876.
- 75 Keitner GI & Rahman S: Reversible neurotoxicity with combined lithium-haloperidol administration. *J Clin Psychopharmacol* 1984; 4:104-105.
- 76 Spring GK: Neurotoxicity with the combined use of lithium and thioridazine. *J Clin Psychiatry* 1979; 40:135-138.
- 77 Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. *J Nerv Ment Dis* 1988; 176:682-685.
- 78 Blake LM, Marks RC, & Luchins DJ: Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 1992; 12:297-299.
- 79 Stevenson RN, Blanshard C, & Patterson DLH: Ventricular fibrillation due to lithium withdrawal - an interaction with chlorpromazine?. *Postgrad Med J* 1989; 65:936-938.
- 80 Miller F & Menninger J: Correlation of neuroleptic dose and neurotoxicity in patients given lithium and a neuroleptic. *Hosp Comm Psychiatr* 1987; 38:1219-1221.
- 81 Chen B & Cardasis W: Delirium induced by lithium and risperidone combination (letter). *Am J Psychiatry* 1996; 153:1233-1234.
- 82 Product Information: LITHOBID(R) slow-release oral tablets, lithium carbonate slow-release oral tablets. JDS Pharmaceuticals, LLC, New York, NY, 2005.
- 83 Amdisen A: Lithium and drug interactions. *Drugs* 1982; 24:133-139.
- 84 Prakash R: Lithium-haloperidol combination and brain damage (letter). *Lancet* 1982; 1:1468-1469.
- 85 Addonizio G, Roth SD, Stokes PE, et al: Increased extrapyramidal symptoms with addition of lithium to neuroleptics. *J Nerv Ment Dis* 1988; 176:682-685.
- 86 Goldney RD & Spence ND: Safety of the combination of lithium and neuroleptic drugs. *Am J Psychiatry* 1986; 143:882-884.

- 87 Carli M, Anand-Srivastava MB, Molina-Holgado E, et al: Effects of chronic lithium treatments on central dopaminergic receptor systems: G proteins as possible targets. *Neurochem Int* 1994; 24:13-22.
- 88 Zall H, Therman PG, & Myers JM: Lithium carbonate: a clinical study. *Am J Psychiatry* 1968; 125:549-555.
- 89 Product Information: Zohydro(TM) ER oral extended-release capsules, hydrocodone bitartrate oral extended-release capsules. Zogenix, Inc. (per FDA), Emeryville, CA, 2013.
- 90 Blumenthal, M, Busse WR, et al Blumenthal, M, Busse WR, et al (Eds): *The Complete German Commission E Monographs*, 1st. American Botanical Council, Austin, TX, 1998, pp 87-88.
- 91 Product Information: Moban(R), Molindone. Endo Pharmaceuticals, Chadds Ford, PA, 1998.
- 92 Product Information: MOBAN(R) oral tablets, molindone HCl oral tablets. Endo Pharmaceuticals Inc., Chadds Ford, PA, 2010.
- 93 Ayd FJ: Psychotropic drug therapy during pregnancy. *Int Drug Ther Newsletter* 1976; 11:5.
- 94 Product Information: Moban(R), Molindone, Endo Pharmaceuticals, Chadds Ford, PA, (PI revised 1/1998) reviewed 11/2000. Moban(R), Molindone, Endo Pharmaceuticals, Chadds Ford, PA, 1998.
- 95 Anon: PDR Physicians' desk reference., Medical Economics Data, Montvale, NJ, 89, pp 922-4.
- 96 Zetin M, Cramer M, Garber D, et al: Bioavailability of oral and intramuscular molindone hydrochloride in schizophrenic patients. *Clin Ther* 1985; 7:169-175.
- 97 Claghorn JL: Psychopharmacologic characteristics of an indole compound - molindone. *Curr Ther Res* 1969; 11:524.
- 98 Shelton J, Prusmach JJ, & Hollister LE: Molindone, a new type of antipsychotic drug. *J Clin Pharmacol* 1968; 8:190.
- 99 Theesen KA, Wilson JE, Newton DW, et al: Compatibility of lithium citrate syrup with 10 neuroleptic solutions. *Am J Hosp Pharm* 1981; 38:1750-1753.
- 100 Product Information: Moban(R), Molindone, Endo Pharmaceuticals, Chadds Ford, PA, (PI revised 1/1998) reviewed 11/2000. Moban(R), Molindone, Endo Pharmaceuticals, Chadds Ford, PA, 1998.
- 101 Ray WA, Chung CP, Murray KT, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360(3):225-235. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 102 Schneeweiss S & Avorn J: Antipsychotic agents and sudden cardiac death — How should we manage the risk?. *N Engl J Med* 2009; 360(3):294-296. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 103 Young LY & Koda-Kimble MA: *Applied Therapeutics: The Clinical Use of Drugs*, Applied Therapeutics, Inc, Vancouver, WA, 1988.
- 104 Appleton WS et al: Before drug therapy begins, choosing an antipsychotic and principles of prescribing antipsychotics. In: Appleton WS ed. *Practical Clinical Psychopharmacology*, 2nd ed, Baltimore: Williams and Wilkins; 1980:1, 1980.
- 105 May PRA: Prediction of schizophrenic patients' response to pharmacotherapy In: Lipton MA & eds: *Psychopharmacology: A Generation of Progress*, Raven Press, New York, 1978, pp 1139.
- 106 Gallant DM, Bishop MP, Steele CA, et al: Molindone: a crossover evaluation of capsule and tablet formulations in severely ill schizophrenic patients. *Curr Ther Res* 1973; 15:915.
- 107 Clark ML, Huber WK, Sakata K, et al: Molindone in chronic schizophrenia. *Clin Pharmacol Ther* 1970; 11:680.
- 108 Greenhill LL, Solomon M, Pleak R, et al: Molindone hydrochloride treatment of hospitalized children with conduct disorder. *J Clin Psychiatry* 1985; 46:20-25.

- 109 Binder R, Glick I, & Rice M: A comparative study of parenteral molindone and haloperidol in the acutely psychotic patient. *J Clin Psychiatry* 1981; 42:203-206.
- 110 Escobar JI, Mann JJ, Keller J, et al: Comparison of injectable molindone and haloperidol followed by oral dosage forms in acutely ill schizophrenics. *J Clin Psychiatry* 1985; 46:15-19.
- 111 Glazer WM, Hafez HM, Benarroche CL, et al: Molindone and haloperidol in tardive dyskinesia. *J Clin Psychiatry* 1985; 46:4-7.
- 112 Ramsay RA, Ban TA, Lehmann HE, et al: A comparative study of molindone and trifluoperazine. *Curr Ther Res* 1970; 12:438.
- 113 Freeman H & Frederick A: Comparison of trifluoperazine and molindone in chronic schizophrenic patients. *Curr Ther Res* 1969; 11:670.
- 114 Simpson GM, Amin M, & Edwards JG: A double blind comparison of molindone and trifluoperazine in the treatment of acute schizophrenia. *J Clin Pharmacol* 1971; 11:227.
- 115 Brauzer B & Goldstein BJ: A clinical comparison of molindone HCl with trifluoperazine in psychotic outpatients. *Curr Ther Res* 1971; 13:152.
- 116 Claghorn JL: Psychopharmacologic characteristics of an indole compound - molindone. *Curr Ther Res* 1969; 11:524.
- 117 Gallant DM & Bishop MP: Molindone: a controlled evaluation in chronic schizophrenic patients. *Curr Ther Res* 1968; 10:441.
- 118 Rickels K, Hutchison J, Morris RJ, et al: Molindone and chlordiazepoxide in anxious neurotic outpatients. *Curr Ther Res* 1972; 14:1-9.
- 119 Carranza-Acevedo J & Tovar-Acosta H: Clinical evaluation of the efficacy of molindone and chlordiazepoxide in anxious outpatients. *Curr Ther Res Clin Exp* 1972; 14:609-614.
- 120 Small JG, Kellams JJ, Dennis JL, et al: Comparison of molindone and tranlycypromine in the treatment of refractory depression. *J Clin Pharmacol* 1981; 21:351-358.
- 121 Jimenez-Jimenez FJ, Garcia-Ruiz PJ, & Molina JA: Drug-induced movement disorders. *Drug Saf* 1997; 16(3):180-204.
- 122 Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): *Pharmacotherapy A Pathophysiologic Approach*, Elsevier, New York, NY, 1989.
- 123 Shader RI & DiMascio A (Eds): *Psychotropic Drug Side Effects*, Williams and Wilkins Company, Maryland, 1977.
- 124 Ereshefsky L & Richards A: Psychoses In: Ereshefsky L & Richards A: Young LY & Koda-Kimble MA: *Applied Therapeutics The Clinical Use of Drugs*, 4th. Applied Therapeutics Inc, Vancouver, WA, 1988.
- 125 Gilman AG, Goodman LS, Rall TW, et al: *Goodman and Gilman's The Pharmacologic Basis of Therapeutics*, 7th ed. Macmillan Publishing, New York, NY, 1985. Jeste DV & Wyatt RJ: Changing epidemiology of tardive dyskinesia: an overview. *Am J Psychiatry* 1981; 138:297-309.
- 126 Khakee A & Hess GF: Mellaril(R) in the treatment of chronically disturbed patients. *Am J Psychiatry* 1960; 116:1029.
- 127 Ananth J: Tardive dyskinesia: myths and realities. *Psychosomatics* 1980; 21:394-396.
- 128 Chien CP: Past history of drug and somatic treatments in tardive dyskinesia In: Fann WE, Smith RC, David JM, et al (Eds): *Tardive Dyskinesia. Research and Treatment*, SP Medical & Scientific Books, New York, NY, 1980, pp 315-324.
- 129 Crane GE: Persistent dyskinesia. *Br J Psychiatry* 1973; 122:395-405.
- 130 Lohr JB, Caligiuri MP, Edson R, et al: Treatment predictors of extrapyramidal side effects in patients with tardive dyskinesia: results from Veterans Affairs Cooperative Study 394. *J Clin Psychopharmacol* 2002; 22(2):196-200.

- 131 Leucht S, Corves C, Arbter D, et al: Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2008; 373(9657):31-41.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 132 Batey SR: Schizophrenic disorders In: DiPiro JT, Talbert RL, Hayes PE, et al (Eds): *Pharmacotherapy A Pathophysiologic Approach*, Elsevier, New York, NY, 1989.
- 133 Mahr GC, Berchou R, & Balon R: A grand mal seizure associated with desipramine and haloperidol. *Can J Psychiatry* 1987; 32:463-464.
- 134 Gilman AG, Goodman LS, Rall TW, et al (Eds): *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 7th. Macmillan Publishing Co, New York, NY, 1985.
- 135 van Sweden B: Neuroleptic neurotoxicity; electro-clinical aspects. *Acta Neurol Scand* 1984; 69:137-146.
- 136 Ereshefsky L & Richards A: Psychoses In: Young LY & Koda-Kimble MA (Eds): *Applied Therapeutics The Clinical Use of Drugs*, 4th. Applied Therapeutics, Inc, San Francisco, CA, 1988.
- 137 AMA Department of Drugs: *AMA Drug Evaluations*, 6th. American Medical Association, Chicago, IL, 1986.
- 138 Markowitz JC & Brown RP: Seizures with neuroleptics and antidepressants. *Gen Hosp Psychiatry* 1987; 9:135-141.
- 139 Owen RR Jr & Cole JO: Molindone hydrochloride: a review of laboratory and clinical findings. *J Clin Psychopharmacol* 1989; 9:268-276.
- 140 James DH: Neuroleptics and epilepsy in mentally handicapped patients. *J Ment Defic Res* 1986; 30:185-189.
- 141 Newcomer JW: Metabolic syndrome and mental illness. *Am J Manag Care* 2007; 13(7 Suppl):S170-S177.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 142 Hasnain M, Vieweg WV, Fredrickson SK, et al: Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications. *Prim Care Diabetes* 2008; Epub:1-.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 143 Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. *J Clin Psychiatry* 2007; 68(Suppl 1):20-27.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 144 Jin H, Meyer JM, & Jeste DV: Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res* 2004; 71(2-3):195-212.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 145 Lieberman JA, Stroup TS, McEvoy JP, et al: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; 353(12):1209-1223.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 146 Stroup TS, Lieberman JA, McEvoy JP, et al: Results of phase 3 of the CATIE schizophrenia trial. *Schizophr Res* 2008; Epub:1.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 147 Marder SR, Essock SM, Miller AL, et al: Physical health monitoring of patients with schizophrenia. *Am J Psychiatry* 2004; 161(8):1334-1349.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 148 None Listed: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27(2):596-601.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>
- 149 Amiel JM, Mangurian CV, Ganguli R, et al: Addressing cardiometabolic risk during treatment with antipsychotic medications. *Curr Opin Psychiatry* 2008; 21(6):613-618.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed> Article: <http://www.ncbi.nlm.nih.gov/...>

- 150 Beers MH, Ouslander JG, Rollinger I, et al: Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med 1991; 151(9):1825-1832.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...>
- 151 Beers MH: Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. Arch Intern Med 1997; 157(14):1531-1536.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...>
- 152 Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med 2003; 163(22):2716-2724.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...>
- 153 Chutka DS , Takahashi PY , & Hoel RW : Inappropriate medications for elderly patients. Mayo Clin Proc 2004; 79(1):122-139.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...>
- 154 Jano E & Aparasu RR : Healthcare outcomes associated with beers' criteria: a systematic review. Ann Pharmacother 2007; 41(3):438-447.PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...PubMed Article: http://www.ncbi.nlm.nih.gov/...>

DRUGDEX is a registered trademark of Thomson Healthcare Inc. All Micromedex Systems are Copyright © Thomson Micromedex. All rights reserved.

The information contained in the Micromedex products is intended as an educational aid only. The information contained in these products is being provided to legal professionals and is not intended for use by legal professionals for patient treatment purposes. All Treatments or procedures are intended to serve as an information resource for physicians or other competent healthcare professionals performing the consultation or evaluation of patients and must be interpreted in view of all attendant circumstances, indications and contraindications. The use of the Micromedex products is at your sole risk. These products are provided "AS IS" and "AS AVAILABLE" for use, without warranties of any kind, either express or implied. Micromedex makes no representation or warranty as to the accuracy, reliability, timeliness, usefulness or completeness of any of the information contained in the products. Additionally, Micromedex makes no representation or warranties as to the opinions or other service or data you may access, download or use as a result of use of the Micromedex products. ALL IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE OR USE ARE HEREBY EXCLUDED. MICROMEDEX DOES NOT ASSUME ANY RESPONSIBILITY OR RISK FOR YOUR USE OF THE MICROMEDEX PRODUCTS.

End of Document

© 2017 Thomson Reuters. No claim to original U.S. Government Works.