

DRUGDEX-EV 2489

MICROMEDEX

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FLURAZEPAM

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0.0] Overview

1) Class

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

Hypnotic

2) Dosing Information

a) [Flurazepam](#) Hydrochloride

1) Adult

a) Insomnia

1) 15 to 30 mg ORALLY at bedtime [1]

2) Pediatric

a) Safety and efficacy in children under age 15 has not been established

3) Contraindications

a) [Flurazepam](#) Hydrochloride

1) hypersensitivity to [flurazepam](#) [10]

2) pregnancy [10]

4) Serious Adverse Effects

a) [Flurazepam](#) Hydrochloride

1) [Granulocytopenic disorder](#)

2j) Leukopenia**5j) Clinical Applications****a) Flurazepam Hydrochloride****1j) FDA Approved Indications****a) Insomnia****1.0j Dosing Information****Drug Properties****Adult Dosage****Pediatric Dosage****1.1j Drug Properties**

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

Bj) Synonyms

Flurazepam

Flurazepam HCl

Flurazepam Hydrochloride

Cj) Physicochemical Properties**1j) Molecular Weight**

aj) Flurazepam: 387.9; Flurazepam monohydrochloride: 424.3; Flurazepam dihydrochloride: 460.8 [308]

2j) pKa

a) 1.9 [309]

1.3j Adult Dosage**1.3.1j Normal Dosage****1.3.1.Aj Flurazepam Hydrochloride****1.3.1.A.1j Insomnia**

a) The recommended dose is 15 to 30 milligrams at bedtime. Dosage should be individualized [1].

b) Efficacy has been maintained for up to 4 weeks of continuous therapy, but long-term treatment with flurazepam is not recommended [1].

1.3.2j Dosage in Renal Failure**Aj) Flurazepam Hydrochloride**

1J) No specific dosage adjustment is necessary in patients with renal failure [6].

2J) Five patients with chronic renal failure developed adverse central nervous system effects which were believed to be in part attributable to flurazepam [7]. The authors suggest that the renal disease of these patients was a probable etiologic factor in the development of the encephalopathy.

1.3.4] Dosage in Geriatric Patients

AJ) Flurazepam Hydrochloride

1J) Elderly patients should be initiated on flurazepam with doses of 15 milligrams since the risk of oversedation, dizziness, confusion, and ataxia increases substantially with larger doses in this population [1] [8] [9].

1.3.5] Dosage Adjustment During Dialysis

AJ) Flurazepam Hydrochloride

1J) No dosage supplement is required following hemodialysis [6].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Flurazepam Hydrochloride

1.4.1.A.1] Insomnia

aJ) No data are currently available for use in children under 15 years of age [5] [1].

1.4.2] Dosage in Renal Failure

AJ) Flurazepam Hydrochloride

1J) No specific dosage adjustment is necessary in patients with renal failure [6].

2J) Five patients with chronic renal failure developed adverse central nervous system effects which were believed to be in part attributable to flurazepam [7]. The authors suggest that the renal disease of these patients was a probable etiologic factor in the development of the encephalopathy.

1.4.4] Dosage Adjustment During Dialysis

AJ) Flurazepam Hydrochloride

1J) No dosage supplement is required following hemodialysis [6].

2.0] Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1] Onset and Duration

AJ) Onset

1)) Initial Response

a)) Hypnotic, oral: 15 to 30 minutes [155].

2)) Peak Response

a)) Hypnotic, oral: 2 to 3 nights [156].

1)) Accumulation of active metabolites may correlate with hypnotic effectiveness with peak effectiveness not occurring until 2 to 3 nights of consecutive drug therapy [156].

B))Duration**1)) Single Dose**

a)) Sedation oral: 10 to 30 hours [157].

2)) Multiple Dose

a)) Hypnotic, oral: 28 nights [158].

1)) Remains effective as a hypnotic for at least 28 consecutive nights [158].

2.2) Drug Concentration Levels**A)) Time to Peak Concentration**

1)) Oral, 30 to 60 minutes [158].

a)) Peak levels of the N-1-hydroxyethylflurazepam occur within 3 to 6 hours [159] and peak levels of N-1-desalkylflurazepam occur at 3 to 48 hours [160].

2.3) ADME**2.3.1) Absorption****A)) Bioavailability**

1)) Oral, capsule: rapidly absorbed [158].

2.3.2) Distribution**A)) Distribution Sites**

1)) Protein Binding

a)) TOTAL PROTEIN BINDING: 97.2% [161].

2.3.3) Metabolism

A) Metabolism Sites and Kinetics

1) Liver [161].

B) Metabolites

1) N-1-hydroxyethylflurazepam, active [158] [161].

2) N-1-desalkylflurazepam, active [158] [161].

2.3.4] Excretion**A) Kidney**

1) Renal Excretion (%)

a) Extensive [158].

2.3.5] Elimination Half-life**A) Parent Compound**

1) ELIMINATION HALF-LIFE

a) 2.3 hours [158].

B) Metabolites

1) N-1-desalkylflurazepam, 47 to 100 hours [158] [160] [161].

2) N-1-hydroxyethylflurazepam, 16 hours [161].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.1] Contraindications**A) [Flurazepam](#) Hydrochloride**

1) hypersensitivity to [flurazepam](#) [10]

2) pregnancy [10]

3.2] Precautions**A) [Flurazepam](#) Hydrochloride**

1) anaphylactic (severe) and [anaphylactoid reactions](#) may occur [10]

2) [angioedema](#) may occur as early as the first dose; permanent discontinuation required [10]

- 3j) chronic pulmonary insufficiency; increased risk of [respiratory depression](#) [10]
- 4j) drug or alcohol abuse, history; increased risk of drug abuse and dependence; monitoring recommended [10]
- 5j) elderly or debilitated patients; increased risk of ataxia or oversedation; dose adjustment recommended [10]
- 6j) [hepatic impairment](#) [10]
- 7j) insomnia (worsening or persisting after 7 to 10 days of treatment) or emergence of new thinking or behavior abnormalities; consider undiagnosed primary psychiatric or physical disorder [10]
- 8j) [renal impairment](#) [10]
- 9j) sleep-related behaviors, complex, have been reported; possibility of patients performing activities while asleep (eg, sleep-driving, making phone calls, preparing/eating food, having sex) with no memory afterwards; increased risk with doses higher than recommended and concomitant use of CNS depressants and alcohol; discontinuation may be necessary if sleep-driving occurs [10]
- 10j) suicidality tendencies, severe depression, or latent depression [10]
- 11j) withdrawal symptoms have occurred following abrupt discontinuation or rapid dose reduction [10]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] [Flurazepam](#) Hydrochloride

3.3.1.A.1] Cardiovascular finding

- a) The manufacturer reports that [flurazepam](#) has caused PALPATATIONS and CHEST PAIN [1].
- b) Heart rate elevation has been observed for up to 4 hours during sleep following the administration of [flurazepam](#) 30 mg or 0.5 mg [triazolam](#). Although this effect appeared to dissipate following continued administration of [triazolam](#), continued [flurazepam](#) administration remained to be associated with an increase in heart rate which was significantly elevated over baseline levels. Although this effect is of little clinical significance in most patients, it indicates that benzodiazepines when given in hypnotic doses, act not only on the central nervous system, but also have peripheral effects [11].

3.3.2] Dermatologic Effects

3.3.2.A] [Flurazepam](#) Hydrochloride

3.3.2.A.1] Skin finding

- a) The manufacturer reports that [flurazepam](#) has caused [PRURITUS](#), SKIN RASH and SWEATING FLUSHING [1].

3.3.4] Gastrointestinal Effects

3.3.4.A] [Flurazepam](#) Hydrochloride

3.3.4.A.1] Disorder of taste

a) The manufacturer reports that [flurazepam](#) has caused BITTER TASTE [1]. [Flurazepam](#) may also cause a metallic taste [13].

3.3.4.A.2] Gastrointestinal tract finding

a) The manufacturer reports that [flurazepam](#) has caused HEARTBURN, UPSET STOMACH, VOMITING, DIARRHEA, CONSTIPATION, GASTROINTESTINAL PAIN, and ANOREXIA. DRY MOUTH and [EXCESSIVE SALIVATION](#) have also been reported [1].

3.3.5] Hematologic Effects

3.3.5.A] [Flurazepam](#) Hydrochloride

3.3.5.A.1] [Anemia](#)

a) The manufacturer reports that [flurazepam](#) has caused in rare instances [LEUKOPENIA](#) and [GRANULOCYTOPENIA](#) [1].

3.3.6] Hepatic Effects

3.3.6.A] [Flurazepam](#) Hydrochloride

3.3.6.A.1] [Hepatotoxicity](#)

a) The manufacturer reports that [flurazepam](#) has caused ELEVATED SGOT/SGPT, ELEVATED TOTAL/DIRECT BILIRUBIN, and ELEVATED [ALKALINE PHOSPHATASE](#) [1].

b) [Cholestatic JAUNDICE](#) is a condition rarely associated with the benzodiazepines. Only 2 cases have been reported secondary to therapy with [flurazepam](#) [14] [15]. A mechanism of injury may be combination of direct [hepatotoxicity](#) and hypersensitivity. An immune response to mild toxic effects in the liver in a susceptible individual has been favored.

c) A 70-year-old male developed [intrahepatic CHOLESTASIS](#) following the administration of oral [flurazepam](#) 30 mg every night for 5 months. The patient was presented with anorexia, weakness, fatigue, brown urine, clay colored stools, palpable liver, and [jaundice](#). Laboratory results were serum [bilirubin](#) 6.6 mg/dL, an [alkaline phosphatase](#) level of 232 IU, an SGOT of 111 IU and serum glutamic pyruvic transaminase (SGPT) of 179 IU, a [blood urea nitrogen](#) (BUN) of 36 mg/dL and a [creatinine](#) of 1.4 mg/dL. Liver biopsy showed [intrahepatic cholestasis](#) with acute and chronic portal inflammation, moderate eosinophils, and some ballooning hepatic cells. The condition of the patient reversed following withdrawal of [flurazepam](#) [14].

d) Acute [INTRAHEPATIC CHOLESTASIS](#) with mild [HEPATOCELLULAR INJURY](#) occurred in a 44-year-old female [15]. The patient had erratically been taking [flurazepam](#) 30 mg at bedtime for approximately 6 months. During the last month, however, medication was taken regularly at bedtime and the patient was taking no other medication. The patient was first seen with a 10-day history of anorexia, nausea, and constant discomfort in the right upper quadrant of the abdomen. She also developed a generalized [pruritus](#) and progressive [jaundice](#) associated with dark urine and pale stools. On admission, the patient's [bilirubin](#) was 8.2 mg/dL, serum glutamic-oxalacetic transaminase (SGOT) 106 IU/L, [alkaline phosphatase](#) 209 IU/L, and gamma-glutamyl transpeptidase ([GGT](#)) 64 IU/L. The patient was withdrawn from [flurazepam](#) therapy at this time. On the fourth day after admission, a [percutaneous liver biopsy](#) revealed mild [hepatocellular injury](#) and acute hepatic [cholestasis](#). The patient's symptoms gradually subsided and liver function has returned to normal. Rechallenge was not performed.

3.3.7] Immunologic Effects

3.3.7.A] Flurazepam Hydrochloride

3.3.7.A.1] Hypersensitivity reaction

a) A 65-year-old male was treated with 30 mg of flurazepam at bedtime for 4 days and developed an allergic reaction characterized by a swollen tongue after 48 hours. After 4 doses of the drug, the swelling became very pronounced and the drug was discontinued. Therapy was switched to chloralhydrate and the tongue reaction disappeared in 24 to 36 hours [20].

3.3.8] Musculoskeletal Effects

3.3.8.A] Flurazepam Hydrochloride

3.3.8.A.1] Musculoskeletal finding

- a) The manufacturer reports that flurazepam has rarely caused BODY/JOINT PAINS [1].
- b) An increased incidence of HIP FRACTURE was reported in elderly patients receiving psychotropic agents [19].

3.3.9] Neurologic Effects

3.3.9.A] Flurazepam Hydrochloride

3.3.9.A.1] Central nervous system finding

a) The manufacturer reports that flurazepam has caused DIZZINESS, DROWSINESS, LIGHT-HEADEDNESS, STAGGERING, ATAXIA, and FALLING [1]. These have particularly occurred in elderly and debilitated patients. Symptoms associated with drug intolerance or overdose include SEVERE SEDATION, LETHARGY, DISORIENTATION, and COMA. Other reported symptoms include: HEADACHE, NERVOUSNESS, TALKATIVENESS, APPREHENSION, IRRITABILITY, WEAKNESS, EUPHORIA, DEPRESSION, SLURRED SPEECH, CONFUSION, RESTLESSNESS, HALLUCINATIONS. PARADOXICAL REACTIONS including EXCITEMENT, STIMULATION, and HYPERACTIVITY have been reported.

b) Five patients received oral flurazepam 30 mg at bedtime for 45 days as a sedative [7]. These patients were on chronic hemodialysis and subsequently developed FORGETFULNESS, SOMNOLENCE, SHORTENED ATTENTION SPAN, IMPAIRED MEMORY and ASTERIXIS. Patients were also noted to be on other drugs which included amitriptyline, hydralazine, and propranolol, pentazocine and diazepam (3 patients). Discontinuation of all the drugs resulted in clearance of the symptoms within 4 to 5 days. These symptoms were reproduced by accidental rechallenge with flurazepam. The authors concluded that these drugs were potentially dangerous in patients with chronic renal failure possibly due to the reduced renal excretion of their metabolites or to some alteration in the metabolism of these compounds.

c) Flurazepam, because of its HANGOVER action, impairs patient performance the morning after drug administration. Driving the morning after a single bedtime dose of flurazepam may be significantly impaired [12]. The effects of repeated daily doses of flurazepam have not been evaluated. Patients should, however, be advised to avoid morning driving until they can determine their individual tolerance and sensitivity.

3.3.10] Ophthalmic Effects

3.3.10.A] Flurazepam Hydrochloride**3.3.10.A.1] Eye / vision finding**

- a) BLURRED VISION, BURNING EYES, and difficulty in focusing has been reported [1].

3.3.11] Otic Effects**3.3.11.A] Flurazepam Hydrochloride****3.3.11.A.1] Ototoxicity**

- a) TINNITUS has been reported [21].

3.3.13] Renal Effects**3.3.13.A] Flurazepam Hydrochloride****3.3.13.A.1] Urogenital finding**

- a) The manufacturer reports that flurazepam has caused GENITOURINARY COMPLAINTS [1].

3.3.15] Respiratory Effects**3.3.15.A] Flurazepam Hydrochloride****3.3.15.A.1] Respiratory finding**

- a) Flurazepam has been associated with significant increases in the number of episodes of sleep apnea and the total duration of APNEA. This is tolerated well by most patients, however, this could be of clinical significance in patients with existing upper airway obstruction [16].
- b) The manufacturer reports that flurazepam has caused SHORTNESS OF BREATH [1].
- c) A 38-year-old male with a history of insomnia and daytime sleepiness normally having 7 to 18 primary obstructive apneic episodes a night experienced a significant rise in the number of episodes to 22 to 100 when receiving flurazepam 30 mg at bedtime. When flurazepam therapy was discontinued, the number of apneic episodes decreased to 6 to 11 per night. This would indicate that normal doses of flurazepam may be a clinically significant problem in susceptible individuals [17].
- d) The administration of flurazepam 30 mg at bedtime did not cause significant oxygen desaturation or breathing disturbances in 17 of 20 patients with chronic obstructive pulmonary disease. The drug did increase total sleep time and appears to be an effective hypnotic in patients with COPD [18].

3.3.16] Other**3.3.16.A] Flurazepam****3.3.16.A.1] Drug withdrawal**

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.B] Flurazepam Hydrochloride**3.3.16.B.1] Withdrawal sign or symptom**

a) Withdrawal symptoms and rebound insomnia have been reported following discontinuation of flurazepam administration [22] [23]. Rebound insomnia has been observed 5 to 7 days after abrupt withdrawal of 15 mg flurazepam in normal subjects who did not suffer from insomnia prior to administration [24]. The incidence of rebound insomnia with flurazepam appears to be less than that observed with shorter acting benzodiazepines, such as triazolam [23].

b) Withdrawal symptoms following abrupt withdrawal of long-term flurazepam therapy (30 mg at bedtime for 8 years) occurred in a 37-year-old male [22]. The patient developed worsening of insomnia, difficulty in falling asleep, dizziness, blurred vision, loss of appetite, gastrointestinal upset, nasal congestion and numbness in the hands and feet. He had been prescribed temazepam 30 mg HS at the same time flurazepam was withdrawn; temazepam partially suppressed the withdrawal symptoms, 3 hours after a dose, but symptoms recurred approximately 12 hours later and persisted for 17 days which resolved upon withdrawing temazepam and again starting flurazepam 30 mg at bedtime. The patient subsequently withdrew flurazepam again, resulting in the same symptoms for a period of 4 weeks.

c) The long term daily use of benzodiazepines (at least 3 months) in therapeutic doses is associated with a mild but significant withdrawal syndrome after discontinuation [21]. Withdrawal symptoms were different than those of anxiety, and included INVOLUNTARY MOVEMENTS, PARESTHESIAS, PERCEPTUAL CHANGES, confusion and persistent tinnitus. Withdrawal symptoms reportedly occurred sooner in patients who had been receiving the shorter-acting benzodiazepines as compared to those receiving longer-acting agents; symptoms resolved after a period of 4 weeks. These data suggest that gradual reduction in the dose of benzodiazepines is indicated for achieving abstinence in outpatients.

d) Benzodiazepine withdrawal symptoms have been reported in patients who received a short-acting benzodiazepine in substitution for a long-acting benzodiazepine [25]. One patient received oxazepam in substitution for diazepam and the other received temazepam in substitution for flurazepam. Both patients received once daily doses of the shorter-acting agent resulting in withdrawal symptoms (insomnia, restlessness, dizziness, nausea, gastrointestinal distress, irritability, blurred vision) which persisted for at least 1 month. If withdrawal symptoms occur after substitution, reintroduction of the longer-acting benzodiazepine is recommended, followed by dosing reductions of 10% per day.

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) Australian Drug Evaluation Committee's (ADEC) Category: C

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Use of flurazepam during pregnancy is contraindicated [146]. All benzodiazepines can be expected to cross the placenta. Although teratogenicity with flurazepam has not been confirmed, other benzodiazepines have demonstrated teratogenic potential [149]. Instruct patients to discontinue flurazepam prior to becoming pregnant. Women of childbearing potential should be warned about the potential risk to the fetus with flurazepam use during pregnancy [146].

If pregnancy occurs during chronic use, the patient should be advised of the desirability of discontinuing the drug and of possible consequences to the fetus. Other benzodiazepines such as [diazepam](#) and [chlordiazepoxide](#) have longer safety records and may be preferred where benzodiazepine use is unavoidable; if given, prescribe as monotherapy in the lowest effective dosage, for the shortest duration possible, and in divided doses to avoid high peak concentrations [150]. In contrast to benzodiazepines, the non-benzodiazepines [zolpidem](#) and [zaleplon](#) are in Pregnancy Risk Categories B and C, respectively [151] [152].

4) Literature Reports

a) A single published report described symptoms of neonatal depression lasting 4 days in an infant exposed during the third trimester to [flurazepam](#). The mother had received 30 milligrams of [flurazepam](#) nightly for 10 days prior to delivery. The neonate appeared hypnotic and inactive, and serum levels of the long-acting metabolite, N1-desalkyl-flurazepam, were detected in the infant, indicating transplacental transfer [146].

b) In a retrospective case control study of 43 pregnant Hungarian women who attempted suicide with nitrazepam or other benzodiazepines (mean nitrazepam dose 204 mg) between 1960 and 1993, 13 of their exposed children were born with congenital abnormalities (30.2%) compared with 3 of their unexposed siblings (10.3%, n=29) (odds ratio 3.8, 95% confidence interval, 1 to 14.6). Congenital abnormalities (CAs) were present in 7 children exposed to nitrazepam alone or with other drugs between postconception weeks 3 and 12, including 3 cases of [congenital inguinal hernia](#), 1 case of torticollis, 1 case of [pectus excavatum](#), complex CA of the respiratory system, and 1 case of multiple CAs with [talipes equinovarus](#), mild [microcephaly](#), and 5 other mild anomalies and borderline fetal alcohol syndrome (FAS). CAs that occurred in the 6 children exposed after postconception week 12 included 2 cases of [congenital inguinal hernia](#), 1 case of bronchial stenosis, and 3 cases of multiple CAs, including FAS with [talipes equinovarus](#) and low IQ; borderline FAS with mild [microcephaly](#) and [talipes equinovarus](#) with 11 minor abnormalities; and [talipes equinovarus](#) with 4 minor abnormalities. Their unexposed siblings with CAs were affected with [cleft lip and palate](#), [ventricular septal defect](#), and FAS. Most CAs were classified as mild deformations. Researchers note concomitant exposure to other drugs, tobacco smoke, and alcohol in several of the exposed children as potential confounds [147].

c) Mixed results were found in a meta-analysis of cohort and case-control studies that reported on the occurrence of major malformations in infants exposed to any benzodiazepine during at least the first trimester of pregnancy [148]. When only cohort studies were pooled, no significant association between benzodiazepine use and major malformations was noted (odds ratio 0.90; 95% confidence interval 0.61 to 1.35; p=0.62); data pooled from case-control studies, however, showed a positive association with major malformations (odds ratio 3.01; 95% confidence interval 1.32 to 6.84; p=0.008). Similar observations were made with regard to oral cleft; the pooled cohort study data did not substantiate an association with drug use (odds ratio 1.19; 95% confidence interval 0.34 to 4.15; p=0.997), whereas the case-controlled data did (odds ratio 1.79; 95% confidence interval 1.13 to 2.82; p=0.01). Finally, the meta-analysis found two case-control studies that each provided conflicting evidence of any association between benzodiazepine exposure and cardiac malformations, and one study failed to find an association between exposure and central nervous system defects.

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)) Human data is lacking regarding the use of [flurazepam](#) during breastfeeding; caution is advised. [Flurazepam](#) has active metabolites with extensive half-lives, which theoretically could accumulate in the nursing infant if passed in breast milk. While the American Academy of Pediatrics identifies a number of benzodiazepines as having unknown effects of possible concern to a nursing infant [153], the World Health Organization considers [diazepam](#) safe during lactation when used occasionally in small doses [154].

3)) Literature Reports

a)) There have been no case reports or published clinical data on the use of [flurazepam](#) in breastfeeding.

4)) Drug Levels in Breastmilk

a)) Active Metabolites

1)) Desalkylflurazepam, hydroxyethylflurazepam [162]

3.5) Drug Interactions

3.5.1) Drug-Drug Combinations

3.5.1.A) [Alfentanil](#)

1)) Interaction Effect: additive [respiratory depression](#)

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: probable

6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7)) Probable Mechanism: CNS depression

8)) Literature Reports

a)) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.B] Amobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.C] Amprenavir

- 1) Interaction Effect: an increased risk of [flurazepam](#) toxicity (excessive sedation, confusion, [respiratory depression](#))
- 2) Summary: Plasma concentrations of [flurazepam](#) may be elevated by the concurrent administration of [amprenavir](#). [Amprenavir](#) is an inhibitor of CYP3A4 isoenzyme. Inhibition of metabolism could result in an increased plasma concentration of [flurazepam](#). Although clinical significance is unknown, a decrease in [flurazepam](#) dosing may be warranted [27].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be exercised if [flurazepam](#) and [amprenavir](#) are administered concurrently. The patient should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [flurazepam](#) metabolism by [amprenavir](#)

3.5.1.D] Anileridine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including

those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.E] Aprobital

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.F] 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 dose of one or both agents [54].

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 dose of one or both agents [54].

7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.G] Butabarbital

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.H] Butalbital

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous

[thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.I] [Carbinoxamine](#)

- 1) Interaction Effect: additive CNS effects
- 2) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects [107] [108]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended [107] [108]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 7) Probable Mechanism: additive effects on the CNS

3.5.1.J] [Carisoprodol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.K] [Chloral Hydrate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: [Chloral](#) hydrate, with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [122]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.L] [Chlorzoxazone](#)

- 1) Interaction Effect: additive [respiratory depression](#)

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.M] [Cimetidine](#)

- 1) Interaction Effect: [flurazepam](#) toxicity (CNS depression)
- 2) Summary: [Cimetidine](#) decreases the clearance of benzodiazepines that are metabolized by hydroxylation or dealkylation (eg, [diazepam](#), [chlordiazepoxide](#), [clorazepate](#), [flurazepam](#), [prazepam](#), [halazepam](#), [alprazolam](#), [triazolam](#), [midazolam](#), [quazepam](#), [estazolam](#), bromazepam) [57] [58] [59] [60]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [61] [62]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, nitrazepam, [clonazepam](#)) [63] [64]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [65] [66] [67] [68].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce benzodiazepine dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: decreased [flurazepam](#) metabolism
- 8) Literature Reports

a) The influence of [cimetidine](#) on the pharmacokinetics of [oxazepam](#), [lorazepam](#), and [flurazepam](#) was evaluated in healthy volunteers [56]. [Cimetidine](#) 300 mg four times daily given concurrently decreased the clearance of [flurazepam](#) but not [oxazepam](#) or [lorazepam](#).

3.5.1.N] [Codeine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a)) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.O| [Dantrolene](#)

1)) Interaction Effect: additive [respiratory depression](#)

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7)) Probable Mechanism: CNS depression

3.5.1.P| [Dong Quai](#)

1)) Interaction Effect: excessive muscle relaxation and central nervous system depression

2)) Summary: Dong quai extract inhibited metabolism of [diazepam](#) and increased its muscle relaxant effect in rats [126]. The effect of dong quai on the metabolism of [diazepam](#) and other benzodiazepines in humans is unknown, as the dose used in the animal study (1 gram/kilogram) is higher than that usually used in humans. Theoretically, if dong quai similarly affects the pharmacokinetics of benzodiazepines in humans, increased levels of benzodiazepine may occur which may result in greater pharmacologic effect of the benzodiazepine. Furocoumarins in dong quai may be responsible for inhibition of hepatic drug metabolism through inhibition of CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation of [diazepam](#) [126]. It is suspected that dong quai may affect other drugs metabolized by the cytochrome P450 enzymes which metabolize [diazepam](#). Caution is advised.

3)) Severity: moderate

4)) Onset: rapid

5)) Substantiation: theoretical

6)) Clinical Management: Monitor patients taking dong quai and benzodiazepines concomitantly for excessive muscle relaxant and sedative effects of benzodiazepines.

7)) Probable Mechanism: inhibition of hepatic cytochrome P450 enzyme metabolism of benzodiazepines

8)) Literature Reports

a)) [Angelica dahurica](#) (dong quai) extract 1 gram/kilogram orally increased the maximum concentration of oral [diazepam](#), yet did not alter pharmacokinetics of intravenous (IV) [diazepam](#) in rats. [Diazepam](#) 5 milligrams/kilogram (mg/kg) was administered orally to rats alone, and one hour after dong quai extract. When administered alone, only the maximum concentration (C_{max}) of [diazepam](#) could be calculated, as the plasma concentration of [diazepam](#) was undetectable at all sample time points except for 2 hours. After dong quai, [diazepam](#) C_{max} increased from 23.0 +/- 12.4 nanograms/milliliter (ng/mL) to 92.1 +/- 50.3 ng/mL (p less than 0.05). [Diazepam](#) pharmacokinetics were not significantly changed by dong quai when [diazepam](#) was administered intravenously. [Diazepam](#) is metabolized by CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation. Dong quai extract inhibited all of these isoenzymes [125].

b) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly increased the muscle relaxant effect of [diazepam](#) (5 mg/kg IV) in rats. Duration of rotarod disruption was increased with high-dose oral dong quai (1 gram/kg) versus [diazepam](#) alone (p less than 0.05). Low-dose oral dong quai (0.3 grams/kg) had no effect on rotarod performance when administered with [diazepam](#) 5 mg/kg IV. Dong quai administered alone had no effect on rotarod performance [125].

3.5.1.Q] [Ethchlorvynol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.R] [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 [121]. 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](#) [53]. 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 [121].
- 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 [121].
- 7) Probable Mechanism: additive CNS depression

3.5.1.S] [Flumazenil](#)

- 1) Interaction Effect: precipitation of seizures
- 2) Summary: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [43].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt

discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [43].

7J) Probable Mechanism: abrupt discontinuation of the anticonvulsant protective effect

3.5.1.TJ Fosamprenavir

1J) Interaction Effect: an increased risk of flurazepam toxicity (excessive sedation, confusion, respiratory depression)

2J) Summary: Plasma concentrations of flurazepam may be elevated by the concurrent administration of fosamprenavir. Amprenavir, the active metabolite of fosamprenavir, is an inhibitor of CYP3A4 isoenzyme. Inhibition of metabolism could result in an increased plasma concentration of flurazepam. Although clinical significance is unknown, a decrease in flurazepam dosing may be warranted [28].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Caution should be exercised if flurazepam and fosamprenavir are administered concurrently. Monitor the patient for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and respiratory depression. A decrease in flurazepam dose may be necessary [28].

7J) Probable Mechanism: inhibition of CYP3A4-mediated flurazepam metabolism by amprenavir, the active metabolite of fosamprenavir

3.5.1.UJ 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 [137].

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 [137].

7J) Probable Mechanism: additive CNS depression

3.5.1.VJ Hydromorphone

1J) Interaction Effect: additive respiratory depression

2J) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [52]. Severe hypotension has been reported with coadministration of midazolam and fentanyl in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either fentanyl or midazolam [53].

3J) Severity: major

4J) Onset: unspecified

- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports
 - a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.W] Kava

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Concomitant use of kava and a benzodiazepine may result in enhanced central nervous system depression. A case report describes a patient experiencing a semicomatose state likely due to concomitant use of kava and [alprazolam](#) [95]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [96].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of kava and benzodiazepines. For patients who choose to use the combination despite this advice, monitor closely for sedation, drowsiness, slowed reflexes, and other indicators of central nervous system depression. Advise against activities that require mental and psychomotor acuity (e.g., handling of heavy machinery).
- 7) Probable Mechanism: additive effects on [GABA](#) receptor binding
- 8) Literature Reports
 - a) A 54-year-old man was hospitalized in a lethargic and disoriented state attributed to concomitant administration of kava with [alprazolam](#) for 3 days. The doses of neither medication were provided. The patient was also taking [cimetidine](#) and [terazosin](#), which can cause confusion and sedation but was apparently not experienced previously in this patient. Blood alcohol level was negative [94].

3.5.1.X] Levorphanol

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a)) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.Y] [Loxapine](#)

1)) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of [respiratory depression](#), hypotension, oversedation, and syncope

2)) Summary: Concomitant use of [loxapine](#), a CNS depressant, and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and other CNS depressants are used concurrently, consider a dose reduction of the CNS depressant [123] and use with caution [124].

3)) Severity: moderate

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [loxapine](#) and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and CNS depressants are used concurrently, consider a dose reduction of the CNS depressant [123] and use with caution [124].

7)) Probable Mechanism: additive CNS depression

3.5.1.Z] [Magnolia](#)

1)) Interaction Effect: increased central nervous system depression

2)) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [102] [103] [104]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [105]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [106]. Therefore, the central nervous system activity of magnolia may be similar to that of benzodiazepines. Caution is advised if magnolia bark and a benzodiazepine are taken concomitantly, as the patient may experience excessive central nervous system depression.

3)) Severity: minor

4)) Onset: delayed

5)) Substantiation: theoretical

6)) Clinical Management: If patients elect to take these compounds concomitantly, they should avoid operating heavy machinery or driving until the magnitude of the effect is known.

7)) Probable Mechanism: possibly stimulation of GABA-A receptors

8)) Literature Reports

a)) Honokiol, a neolignane derivative present in magnolia bark, has central nervous system depressant activity and at lower doses, anxiolytic activity. Anxiolytic activity (as shown by prolonged time spent in the open arms of the maze) was noted in a plus-maze test in mice of a single oral dose of 20 milligrams/kilogram (mg/kg) honokiol (p less than 0.05). Honokiol did not affect traction performance, whereas [diazepam](#) 0.5 mg/kg to 2 mg/kg prolonged time spent in open arms of the maze and disrupted traction performance. After 7 days of treatment with 0.2 mg/kg honokiol and after a single treatment with 1 mg/kg [diazepam](#), performance in the plus-maze was nearly equivalent. The effect of honokiol was reversed following subcutaneous administration of [flumazenil](#) 0.3 mg/kg. Combination treatment with honokiol and [diazepam](#) significantly prolonged the time spent in open arms of the maze over treatment with either alone (p less than 0.05). Honokiol reduced the effect of [diazepam](#) on motor activity, but did not affect diazepam-induced inhibition of traction performance. The authors concluded based on

their findings that honokiol induces an anxiolytic effect with less liability of causing sedation, disinhibition, or motor dysfunction than [diazepam](#). Possible mechanisms proposed were that honokiol selectively stimulates GABA-A receptors, or honokiol binds to other sites related to the anxiolytic effect [97].

b)) Honokiol administered intravenously to 5 rats resulted in an elimination rate constant of 0.08 ± 0.01 Liters/minute (L/minute) after a 5 mg/kg loading dose, and 0.06 ± 0.02 L/minute after a 10 mg/kg loading dose. Half-life was 49.22 \pm 6.78 minutes after a 5 mg/kg loading dose, and 56.24 \pm 7.30 minutes after a 10 mg/kg loading dose. The bioavailability as expressed as area under the curve (AUC) was 58.87 \pm 4.19 micrograms/milliliter/minute (mcg/mL/minute) after a 5 mg/kg loading dose, and 133.89 \pm 16.26 mcg/mL/minute (p less than 0.05) after a 10 mg/kg loading dose [98].

c)) Magnolol and honokiol at 100 mg/kg, 200 mg/kg, and 400 mg/kg administered intraperitoneally to mice suppressed grip strength in a dose-dependent manner. Grip strength was lost within 30 minutes, which was sustained for 3 hours after a 400 mg/kg dose of either compound. Spinal reflexes in the chick were inhibited in a dose-dependent manner with magnolol and honokiol at 12.5 mg/kg, 25 mg/kg, 50 mg/kg, and 100 mg/kg intraperitoneally [99].

d)) Magnolol and honokiol may cause depression of the ascending activating systems and the spinal cord based on mice studies demonstrating sedation, ataxia, muscle relaxation, and anticonvulsant activities of magnolol and honokiol. Magnolol at 63 mg/kg intraperitoneally produced [hypomotility](#), [ptosis](#), and sedation. Magnolol 125 mg/kg produced sedation, ataxia, and muscle relaxation; at 250 mg/kg magnolol produced ataxia, loss of righting reflex, and muscle relaxation of 4 legs. Honokiol produced similar effects at 125 mg/kg, 250 mg/kg, and 500 mg/kg. Both magnolol and honokiol compounds at 50 mg/kg suppressed spinal reflexes in chicks. In mice, pretreatment with magnolol 100 mg/kg inhibited tonic extensor convulsion and death induced by an intracerebroventricular injection of [penicillin G](#) potassium 50 micrograms (mcg) [100].

e)) The ether extract of magnolia bark and its purified constituents, magnolol and honokiol were examined in terms of muscle relaxant properties in the mouse model. Magnolol at 100 mg/kg produced muscle relaxation for 2 hours; magnolol 250 mg/kg induced loss of righting reflex and muscle relaxation extending beyond 3 hours. Honokiol 250 mg/kg exhibited muscle relaxation properties for 3 hours with 500 mg/kg producing loss of righting reflex. Muscle relaxing properties of both compounds subsided fully within 24 hours after injection. The ether extract at 1 gram/kg induced loss of righting reflex 30 minutes after injection for nearly 60 minutes [101].

3.5.1.AA] [Meclizine](#)

1)) Interaction Effect: an increase in CNS depression or [respiratory depression](#)

2)) Summary: Concomitant use of [meclizine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives may potentiate CNS depression cognitive and motor effects. Avoid concurrent use of alcohol while taking [meclizine](#) [117] [118] [119] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Concomitant use of [meclizine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may potentiate CNS depression. Avoid concurrent use of alcohol with [meclizine](#) [117] [118] [119] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

7J) Probable Mechanism: additive effects

3.5.1.AB] Meperidine

1J) Interaction Effect: additive [respiratory depression](#)

2J) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

8J) Literature Reports

aJ) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AC] Mephesisin

1J) Interaction Effect: additive [respiratory depression](#)

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

3.5.1.AD] Mephobarbital

1J) Interaction Effect: additive [respiratory depression](#)

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

6J) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

8J) Literature Reports

aJ) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity),

while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AE] [Meprobamate](#)

1)) Interaction Effect: additive [respiratory depression](#)

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7)) Probable Mechanism: CNS depression

3.5.1.AF] [Metaxalone](#)

1)) Interaction Effect: additive [respiratory depression](#)

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].

3)) Severity: major

4)) Onset: unspecified

5)) Substantiation: theoretical

6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7)) Probable Mechanism: CNS depression

3.5.1.AG] [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 [49].

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 [49].

7) Probable Mechanism: additive CNS depression effects

3.5.1.AH] [Methocarbamol](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [131] [132] [133] [134].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.AI] [Methohexital](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AJ] [Mirtazapine](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of [mirtazapine](#) and any benzodiazepine has additive CNS depressive effects. When [diazepam](#) was coadministered with [mirtazapine](#) in 12 healthy patients, [diazepam](#) had minimal effects on plasma levels of [mirtazapine](#). However, because the motor-skill impairment is additive, concomitant use should be avoided [55].

3) Severity: major

4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [mirtazapine](#) and any benzodiazepine should be avoided due to additive CNS depression [55].
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports
 - a) When [diazepam](#) 15 mg was coadministered with [mirtazapine](#) 15 mg in 12 healthy patients, [diazepam](#) had minimal effects on plasma levels of [mirtazapine](#). However impaired motor skills is additive [55].

3.5.1.AK] [Morphine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports
 - a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AL] [Morphine Sulfate Liposome](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports
 - a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AM] Oxycodone

- 1) Interaction Effect: increased CNS or [respiratory depression](#)
- 2) Summary: Concomitant use of [oxycodone](#) with other CNS depressants, such as benzodiazepines, may result in [respiratory depression](#), hypotension, profound sedation, coma, or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#) controlled-release tablets at one-third to one-half of the usual dosage [112] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [113].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxycodone](#) with other CNS depressants, such as benzodiazepines, may result in [respiratory depression](#), hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate [oxycodone](#) controlled-release tablets at one-third to one-half of the usual dosage [112] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [113].
- 7) Probable Mechanism: additive effects

3.5.1.AN] Oxymorphone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AO] Passionflower

- 1) Interaction Effect: additive CNS depression
- 2) Summary: In one case report, valerian and passionflower used concurrently with [lorazepam](#) resulted in additive CNS depressive effects. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors . It is recommended that patients be asked about herbal product use during intake of personal history [84]. Monitor for increased CNS depressive adverse effects if passionflower is coadministered with a benzodiazepine.
- 3) Severity: moderate
- 4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of passionflower and benzodiazepines may result in additive CNS depressive effects. It is recommended that patients be asked about herbal product use during intake of personal history [84]. Monitor for increased CNS depressive adverse effects if passionflower is coadministered with a benzodiazepine.

7) Probable Mechanism: additive effects on the benzodiazepine receptor

8) Literature Reports

a) A case report describes a potentiated CNS depressive effect in a 40-year-old man following concomitant use of [lorazepam](#) with valerian and passionflower. The patient, who had been treating with [lorazepam](#) 2 mg/day for 2 months with no adverse effects, self-administered an infusion of valerian subterranean parts (estimated dose, 300 mg). 2 hours before going to bed for 2 consecutive days. On day 3, he instead ingested 3 oral tablets of dry extract from valerian rhizomes (300 mg/tablet) plus roots and aerial parts of passionflower (380 mg/tablet) at 1 hour intervals before bedtime. Nervousness and mild shaking dissipated after going to bed followed by extreme somnolence. After taking the same dose of the valerian root/passionflower product on day 4, he experienced more severe symptoms including substantial hand shaking, dizziness, and palpitations before bedtime followed by profound somnolence. Upon presentation after 32 hours of experiencing these CNS symptoms, he was observed to have nervousness while speaking and demonstrated anxious behavior without shaking. He had a history of general anxiety disorders and dream disorders. His family history was negative for essential tremor and there were no metabolic, [renal](#), or [hepatic disorders](#), [high blood pressure](#), or drug allergies. Because a drug interaction was suspected, the patient was continued on [lorazepam](#) but withdrawn from valerian and passionflower and symptoms resolved. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors [84].

b) Chrysin (5,7-di-OH-flavone), a flavonoid in *Passiflora coerulea*, was identified as a naturally-occurring benzodiazepine receptor ligand in plants obtained from local sources at the Universidad de Buenos Aires [109]. However, in a [high performance liquid chromatography](#) analysis sensitive to a detection limit of 1 part per million (ppm), chrysin could not be detected in an ethanolic extract of aerial parts of *Passiflora coerulea* obtained from the botanical garden of the University of Bologna or in a *Passiflora incarnata* fluid extract prepared according to the Italian Pharmacopoeia, IX edition [110]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [111].

3.5.1.AP] [Pentobarbital](#)

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity),

while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AQ] Perampanel

- 1)) Interaction Effect: potentiation of impaired cognitive and motor effects
- 2)) Summary: Caution is advised if perampanel is coadministered with CNS depressants. Although not studied with other CNS depressants, perampanel had additive or supra-additive effects to alcohol on complex tasks (eg, driving), enhanced alcohol's effect on alertness and vigilance, and increased levels of anger, confusion, and depression in a pharmacodynamic study with healthy volunteers. Concomitant use of perampanel may potentiate the impaired cognitive and motor effects of CNS depressants [135].
- 3)) Severity: moderate
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Caution is advised if perampanel is coadministered with CNS depressants. Concomitant use of perampanel may potentiate the impaired cognitive and motor effects of CNS depressants [135].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.AR] Phenobarbital

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: probable
- 6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression
- 8)) Literature Reports

a)) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it

follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AS] [Primidone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AT] [Propoxyphene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AU] [Remifentanyl](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [52]. Severe hypotension has been reported with coadministration of [midazolam](#) and [fentanyl](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.AV] [Ritonavir](#)

- 1) Interaction Effect: an increased risk of extreme sedation, [respiratory depression](#) and confusion
- 2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [flurazepam](#), causing a potential risk of extreme sedation and [respiratory depression](#) [138]. A decrease in benzodiazepine dose may be needed [139].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for signs and symptoms of benzodiazepine toxicity (sedation, confusion, [respiratory depression](#)). Reduce doses of [flurazepam](#) as required.
- 7) Probable Mechanism: increased [flurazepam](#) serum concentrations due to decreased [flurazepam](#) metabolism

3.5.1.AW] [Saquinavir](#)

- 1) Interaction Effect: increased [flurazepam](#) plasma concentrations
- 2) Summary: Coadministration of [saquinavir](#) (strong CYP3A4 inhibitor) and a benzodiazepine, such as [flurazepam](#), may result in increased benzodiazepine plasma concentrations. If the concomitant use of [flurazepam](#) with [saquinavir](#) is necessary, consider dose reductions of [flurazepam](#) when necessary [116].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [flurazepam](#) and [saquinavir](#) may lead to increased [flurazepam](#) plasma concentrations. If coadministration is required, a dose reduction of [flurazepam](#) may be warranted [116].
- 7) Probable Mechanism: unknown

3.5.1.AX] [Secobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.AY] Skullcap

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: In vitro studies demonstrate that several constituents of skullcap have affinity for the benzodiazepine binding site of the GABA-A receptor, and appear to compete with benzodiazepines for the site [129] [130]. Theoretically, skullcap may have additive effects when administered with a benzodiazepine, yet if the binding is competitive in nature, skullcap may displace the benzodiazepine from the receptor and reduce its effectiveness. Caution is advised with concomitant use of skullcap and benzodiazepines until this potential interaction is better characterized.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for increased central nervous system depression, and for altered effectiveness of benzodiazepine therapy.
- 7) Probable Mechanism: several constituents of skullcap have demonstrated binding affinity for the benzodiazepine site of the GABA-A receptor
- 8) Literature Reports

a) Constituents isolated from the organic solvent extract of skullcap root demonstrated binding affinity for the benzodiazepine (BZD) site of the GABA-A receptor. Wogonin and baicalein had the strongest affinity, scutellarein had moderate activity, and baicalin had weakest activity. All of these constituents contain the flavonoid phenylbenzopyrone nucleus, which binds to the benzodiazepine site. The concentrations at which 50 percent inhibition (IC₅₀) of (3H)flunitrazepam binding occurred were as follows, wogonin 3.62 micromolar (mcM); baicalein 10.11 mcM; scutellarein 20.96 mcM; and baicalin 137.07 mcM, whereas the IC₅₀ of [diazepam](#) was 0.029 mcM [127].

b)) Constituents isolated from the water extract of skullcap root demonstrated activity on the [dopamine](#) D1, D2, 5-hydroxytryptamine, and benzodiazepine (BDZ) binding sites of gamma-amino butyric acid ([GABA](#)) receptors, but not on muscarinic [acetylcholine](#) M1, 5-HT2 receptors or the [GABA](#) binding site of [GABA](#) receptors in vitro. Baicalein, oroxylin A and wogonin, flavone constituents of skullcap, showed weak binding to the BDZ sites while skullcapflavone II demonstrated binding comparable to that of [chlordiazepoxide](#) but 100-fold less than [flurazepam](#) [128].

3.5.1.AZ] [Sodium Oxybate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [26]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression

3.5.1.BA] [St John's Wort](#)

- 1)) Interaction Effect: reduced benzodiazepine effectiveness
- 2)) Summary: Concomitant use of [alprazolam](#), [midazolam](#), or [quazepam](#) (all CYP3A4 substrates) with St. John's wort (CYP3A4 inducer) was shown to induce benzodiazepine metabolism in trials of healthy participants [44] [45] [46] [47]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [44]. Because other benzodiazepines are also CYP3A4 substrates, similar results can be expected when another benzodiazepine is coadministered with St. John's wort. Monitoring benzodiazepine plasma concentrations and efficacy may be warranted if used concomitantly with St. John's wort. If a patient is taking St. John's wort at the time of surgery during which [midazolam](#) or any other benzodiazepine is to be used for sedation, it may be necessary to monitor the patient for signs of decreased benzodiazepine efficacy and adjust the benzodiazepine dose when needed.
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: established
- 6)) Clinical Management: Concomitant use of [alprazolam](#), [midazolam](#), or [quazepam](#) with St. John's wort was shown to induce the CYP3A4-mediated metabolism of the benzodiazepine in studies of healthy participants [44] [45] [46] [47]. Because benzodiazepines are metabolized by CYP3A4 pathways, similar results would be expected if any benzodiazepine was coadministered with St. John's wort. Therefore, consider monitoring for alterations in the therapeutic and adverse effects of the benzodiazepine if used concomitantly with St. John's wort. If a patient is taking St. John's wort at the time of surgery during which [midazolam](#) or any other benzodiazepine is to be used for sedation, consider monitoring the patient closely for signs of reduced benzodiazepine effectiveness and adjusting the benzodiazepine dose, if necessary.
- 7)) Probable Mechanism: induction of CYP3A4-mediated metabolism of the benzodiazepine by St. John's wort
- 8)) Literature Reports

a)) Concomitant use of [quazepam](#) and St. John's wort decreased [quazepam](#) plasma concentrations, but did not affect [quazepam](#) efficacy, in a randomized, double-blind, placebo-controlled, crossover study of 13 healthy adult males. Participants refrained from grapefruit-containing products and

herbal supplements or tea; caffeine-containing products were withheld. Participants received either oral St. John's wort (standardized to 0.3% hypericin) 300 mg 3 times/day or placebo for 14 days. On day 14, a single [quazepam](#) 15-mg oral dose was given. Blood samples were obtained just prior to and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hrs after the [quazepam](#) dose. At 48 hrs, [quazepam](#) Cmax and AUC were reduced by 8.7 nanograms (ng)/mL (95% confidence interval (CI), -17.1 to -0.2 ng/mL; p less than 0.05) and by 55 ng hr/mL (95% CI, -96 to -15 ng hr/mL; p less than 0.05), respectively, in the St. John's wort group compared with the placebo group. [Quazepam](#) Tmax and t(1/2) and 2-oxoquazepam Cmax, AUC, Tmax, and t(1/2) were not significantly affected by St. John's wort. The 2-oxoquazepam to [quazepam](#) ratio in the Cmax was higher in the St. John's wort group compared with the placebo group (0.47 vs 0.4 ng/mL; p less than 0.01). The urinary ratio of 6-beta-hydroxycortisol to cortisol was increased with St. John's wort compared with placebo (ratio, 2.1; 95% CI, 0.85 to 3.4; p less than 0.05); an increased urinary ratio of cortisol metabolite to cortisol is indicative of hepatic CYP3A4 activity. [Quazepam](#) efficacy was not significantly changed with the coadministration of St. John's wort as reflected in the visual analogue scale (VAS), which evaluates self-ratings of sedative-like effects, and the digit symbol substitution test (DSST) which measures psychomotor performance [44].

b)) St. John's wort significantly reduced the bioavailability of [midazolam](#) by 50% after 12 days in an open-label, crossover study of 22 healthy subjects. Subjects received St. John's wort (Jarsin 300, LI 160, Lichtwer Pharma) 300 mg three times daily for 12 days followed by a single dose of [midazolam](#) 4 mg orally or 1 mg intravenously. Oral clearance of [midazolam](#) was increased by 168%, and maximum concentration was reduced by 53% (both p less than 0.0001) [45].

c)) St. John's wort significantly induced the metabolism of [midazolam](#) after 4 weeks in a randomized, open-label trial of 12 healthy subjects. Subjects received St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg orally three times daily for 28 days. The St. John's wort was from a single lot but was not tested to verify label claims. Subjects received oral [midazolam](#) 8 mg prior to supplementation and on day 27. St. John's wort increased the mean 1-hour 1-hydroxymidazolam/[midazolam](#) ratio by 98% (p less than 0.0001), indicating induction of CYP3A4. Female subjects experienced a 74% greater increase than males (p = 0.029). In males, the rate of metabolism correlated with body mass index [48].

d)) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and Cmax of oral [midazolam](#) were reduced by 50%, and oral clearance increased 2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [46].

e)) St. John's wort significantly increased the plasma clearance of [alprazolam](#), (studied as a CYP3A4 probe drug). In an open-label, crossover study, healthy adult subjects (n=12) received a single, oral dose of St. John's wort 300 mg (standardized to 0.12% to 0.3% hypericin (LI 160, Kira(R))) 3 times daily for 14 days, followed by another single dose of oral [alprazolam](#) 2 mg. Compared with baseline, St. John's wort induced a 2-fold increase in plasma clearance of

alprazolam (p less than 0.001) and a 2-fold decrease in AUC for alprazolam (p less than 0.001). Alprazolam elimination half-life was also reduced (from 12.4 to 6 hours; p less than 0.001) [47].

3.5.1.BB| Sufentanil

- 1) Interaction Effect: additive respiratory depression
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [51]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [52]. Severe hypotension has been reported with coadministration of midazolam and fentanyl in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either fentanyl or midazolam [53].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for respiratory depression when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression
- 8) Literature Reports

a) Concomitant propoxyphene (65 mg every six hours) and alprazolam (1 mg) therapy has been reported to increase the half-life of alprazolam by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [50].

3.5.1.BC| Suvorexant

- 1) Interaction Effect: CNS depression
- 2) Summary: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [83].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of suvorexant with other CNS depressants due to the risk of additive CNS depressant effects. Cognitive and behavioral changes (eg, hallucinations, anxiety, amnesia, other neuropsychiatric symptoms) and complex sleep behaviors (eg, sleep-driving, preparing and eating food) may also be potentiated. Also alcohol should be avoided during treatment. If coadministration with another CNS depressant is required, dose adjustments of both drugs may be necessary. Concurrent use with other medications that treat insomnia is not recommended, and suvorexant discontinuation may be required if complex sleep behaviors develop [83].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BD| Tan-Shen

- 1) Interaction Effect: increased risk of central nervous system depression
- 2) Summary: Miltirone and the other nine diterpene quinones present in Salvia miltiorrhiza (Tan-shen) appear to act as partial agonists at central benzodiazepine receptors [115]. While this is likely responsible

for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [115]. Because tan-shen acts as a partial and not a full agonist, the clinical significance of the interaction is unknown. Caution is advised until the magnitude of the interaction is better understood.

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if tan-shen is used concomitantly with a benzodiazepine. Patients should be advised to avoid operating heavy machinery until the magnitude of the interaction is known.

7) Probable Mechanism: partial agonist activity at central benzodiazepine receptors

8) Literature Reports

a) Ten diterpene quinones present in the Chinese medicinal herb *Salvia miltiorrhiza* (tan-shen) have been shown to inhibit binding of (3H) flunitrazepam to central benzodiazepine receptors. These quinones, isolated from the ethereal extract of the roots of *Salvia miltiorrhiza*, exhibited IC₅₀s ranging from 0.3 to 36.2 μmol (the IC₅₀ is the drug concentration required to provide 50% inhibition of specific (3H) flunitrazepam binding). Miltirone had the highest potency (IC₅₀=0.3 μmol) [114]. Oral administration of miltirone (10-60 mg/kg) increased the number of punished crossings of mice in the Four-Plate Test which is an indication of clinical tranquilizing effects. The magnitude of this effect was lower than that observed with [diazepam](#) [114].

3.5.1.BE] Tapentadol

1) Interaction Effect: an increase in central nervous system and [respiratory depression](#)

2) Summary: The concomitant use of tapentadol with central nervous system depressants including sedatives (eg, [alprazolam](#), [midazolam](#), or [zolpidem](#)) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma. When administering tapentadol and a sedative together, dosage of one or both agents may be reduced [120].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when tapentadol and sedatives are used in combination. A reduction in dose of one or both drugs may be necessary [120].

7) Probable Mechanism: additive effects

3.5.1.BF] Teduglutide

1) Interaction Effect: increased exposure of orally administered benzodiazepines

2) Summary: Coadministration of teduglutide with an oral medication that requires titration, such as a benzodiazepine, may significantly increase absorption of the benzodiazepine. In clinical trials, a patient taking a benzodiazepine who was treated with concomitant teduglutide experienced altered mental status that progressed to coma. A reduced dose of oral drugs requiring titration (eg, benzodiazepines) may be necessary when administered concomitantly with teduglutide [93]. If coadministration is necessary, the patient should be monitored for increased benzodiazepine side effects.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if teduglutide is coadministered with an oral medication that requires titration, such as a benzodiazepine. Concomitant use may cause increased absorption of benzodiazepines and require dose adjustment of the orally administered benzodiazepine [93]. Monitor

for increased benzodiazepine side effects if a patient is taking teduglutide concomitantly with an oral benzodiazepine.

7J) Probable Mechanism: unknown

8J) Literature Reports

aJ) In a placebo-controlled clinical trial of teduglutide in adults with [short bowel syndrome](#) who were dependent on parenteral nutrition support, 1 woman who received teduglutide 0.05 mg/kg/day with concomitant oral [prazepam](#) had a dramatic deterioration in mental status, progressing to coma during the first week of study treatment. The level of [prazepam](#) in her blood was more than 300 mcg/L upon being admitted to the ICU. The coma resolved 5 days after teduglutide and [prazepam](#) were discontinued [93].

3.5.1.BG| [Theophylline](#)

1J) Interaction Effect: decreased benzodiazepine effectiveness

2J) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [38] [39] [40] [41]. A larger dose of benzodiazepine may be needed to produce sedation in a theophylline-treated patient. [Respiratory depression](#) may occur if [theophylline](#) is discontinued without a reduction of the benzodiazepine dose [42].

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Monitor the patient for benzodiazepine clinical effectiveness. A larger than usual benzodiazepine dose may be required in a theophylline-treated patient. Benzodiazepine toxicity ([respiratory depression](#), sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) may occur if [theophylline](#) is discontinued without a subsequent reduction in the benzodiazepine dose.

7J) Probable Mechanism: [theophylline](#) blocks [adenosine](#) receptors

8J) Literature Reports

aJ) Eight healthy male volunteers participated in a study which demonstrated the antagonistic properties of [theophylline](#) on diazepam-induced [psychomotor impairment](#). Subjects received an oral dose of [diazepam](#) 0.25 mg/kg, followed 40 minutes later by an intravenous infusion of 100 mL normal saline with or without [theophylline](#) 4.4 mg/kg. All subjects were tested twice: one time receiving [theophylline](#) and the other time receiving placebo. [Theophylline](#) reversed some of the diazepam-induced [psychomotor impairment](#) as measured by the digit symbol substitution test, card sorting, and three questionnaires which measured mood, anxiety, and distress. The antagonism caused by [theophylline](#) may be attributed to the stimulant action caused by methylxanthines on the central nervous system through [adenosine](#) receptor blockade [29].

bJ) Intravenous [theophylline](#) was reported to reverse the sedation produced by intravenous [diazepam](#) in patients undergoing [genitourinary surgery](#). Patients were given intravenous doses of [diazepam](#) during surgery to maintain deep sedation, followed by administration of intravenous [aminophylline](#) (60 to 120 mg) or normal saline postoperatively. Rapid [reversal of sedation](#) occurred in [aminophylline](#) patients as compared to no response in saline patients [30]. Other studies and case reports have also shown that [theophylline](#) antagonizes the sedative effects of [diazepam](#) [31] [32].

cJ) Three case reports described patients who had the sedative effects of [lorazepam](#) reversed postoperatively by the administration of [aminophylline](#) 1 mg/kg intravenously [33]. This same [aminophylline](#) dose was used to reverse the sedative effects of [midazolam](#) in three other patients

[34]. [Theophylline](#) also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [35].

d) Less successful rates have been reported when utilizing [aminophylline](#) to reverse benzodiazepine oversedation. Of the six patients reported, all of whom had received [midazolam](#), five patients showed no change in the level of consciousness after the administration of [aminophylline](#) 75 mg. One patient did experience quick and sudden awakening after [aminophylline](#) was given. The author suggests that there may be wide individual variations within the population to the effects of [aminophylline](#) antagonism on benzodiazepines [36].

e) To determine the mechanism by which [theophylline](#) antagonizes benzodiazepines, oral [alprazolam](#) 1 mg daily for seven days was administered to six patients who were receiving [theophylline](#) and to seven patients who were not receiving [theophylline](#) treatment. Serum [alprazolam](#) levels were significantly lower in patients on concurrent [theophylline](#) therapy, and the levels continued to decrease during each day of the study. In patients who were not receiving [theophylline](#), serum [alprazolam](#) levels were within the therapeutic range. The authors concluded that the antagonism of the anxiolytic effects of benzodiazepines by [theophylline](#) may be due to decreased serum benzodiazepine levels in these patients [37].

3.5.1.BH] Thiopental

1) Interaction Effect: additive [respiratory depression](#)

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [78] [79] [80] [81] [82].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

8) Literature Reports

a) It has been noted in several studies that combinations of [clonazepam](#) and [primidone](#) or [phenobarbital](#) tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while [clonazepam](#) in combination with hydantoins or [carbamazepine](#) are better tolerated [69] [70] [71] [72] [73].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [74]. The combination of intravenous [thiopental](#) and [midazolam](#) had 1.8 times the expected potency of the individual drugs, and the dose of [thiopental](#) required to produce [anesthesia](#) was reduced by 50% in another study [75]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [76]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [77].

3.5.1.BI] Valerian

1) Interaction Effect: additive CNS depression or reduced effectiveness of the benzodiazepine

2) Summary: In one case report, valerian and passionflower used concurrently with [lorazepam](#) resulted in additive CNS depressive effects [84]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [92] [85]. Valerian extract

displaced the benzodiazepine fluorodiazepam from the receptor [85]. The clinical effect may be additive or reduced effectiveness of benzodiazepines depending on the nature of the binding. It is recommended that patients be asked about herbal product use during intake of personal history [84]. Monitoring for altered effectiveness of the benzodiazepine should be considered with concurrent use.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of valerian and benzodiazepines may result in additive CNS depressive effects or may decrease the effectiveness of benzodiazepines. It is recommended that patients be asked about herbal product use during intake of personal history [84] [85]. Monitor for altered effectiveness of the benzodiazepine during concurrent use.

7) Probable Mechanism: additive effects on the benzodiazepine receptor, possible displacement of the benzodiazepine from its receptor

8) Literature Reports

a) A case report describes a potentiated CNS depressive effect in a 40-year-old man following concomitant use of [lorazepam](#) with valerian and passionflower. The patient, who had been treating with [lorazepam](#) 2 mg/day for 2 months with no adverse effects, self-administered an infusion of valerian subterranean parts (estimated dose, 300 mg). 2 hours before going to bed for 2 consecutive days. On day 3, he instead ingested 3 oral tablets of dry extract from valerian rhizomes (300 mg/tablet) plus roots and aerial parts of passionflower (380 mg/tablet) at 1 hour intervals before bedtime. Nervousness and mild shaking dissipated after going to bed followed by extreme somnolence. After taking the same dose of the valerian root/passionflower product on day 4, he experienced more severe symptoms including substantial hand shaking, dizziness, and palpitations before bedtime followed by profound somnolence. Upon presentation after 32 hours of experiencing these CNS symptoms, he was observed to have nervousness while speaking and demonstrated anxious behavior without shaking. He had a history of general anxiety disorders and dream disorders. His family history was negative for essential tremor and there were no metabolic, [renal](#), or [hepatic disorders](#), [high blood pressure](#), or drug allergies. Because a drug interaction was suspected, the patient was continued on [lorazepam](#) but withdrawn from valerian and passionflower and symptoms resolved. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors [84].

b) The amount of the amino acid [gamma-aminobutyric acid \(GABA\)](#) in aqueous and hydroalcoholic extracts of valerian is sufficient to explain its (3H)muscimol displacement effect at [GABA](#) receptor sites during in vitro tests. The [GABA](#) content of the aqueous extract is also sufficient to cause release of (3H)[GABA](#) in synaptosomes through homologous exchange, accounting for this in vitro effect as well. Since [GABA](#) cannot effectively cross the blood-brain barrier when given in the amounts available in the extracts, it appears unlikely that the influence of valerian on [GABA](#) neurotransmission contributes to central nervous system sedation [86] [87]. Valeriana officinalis extracts significantly displaced fluorodiazepam from benzodiazepine receptors, and a fraction containing sesquiterpene alcohols and ketones showed 80% inhibition at concentrations of 1.5×10^{-3} moles/liter. A fraction containing valepotriates also produced significant displacement. Statistical values were not provided [88]. In local cerebral glucose utilization, valerian extracts reacted in a way analogous to that observed with the [GABA](#) agonist, progabide. Therefore, the interaction at the GABA-A-benzodiazepine receptor complex may differ from that of [diazepam](#) [89]. Valerian extracts inhibit (3H)flunitrazepam binding to benzodiazepine receptors; however, the amount of benzodiazepine-like molecules present in the plants is below pharmacologically-active doses [90].

c) Hydroalcoholic and aqueous extracts of *Valeriana officinalis* roots showed affinity for the GABA-A receptors with lesser affinity for the peripheral benzodiazepine receptors in vitro. Inhibition of 3H-PK 11195 binding to benzodiazepine and GABA-A receptors was measured and expressed as IC50 values. IC50 values for the hydroalcoholic extract were 0.04 milligrams/milliliter (mg/ml) and 3.9×10^{-3} mg/ml for peripheral and central benzodiazepine receptors and GABA-A receptors, respectively. The lipophilic fraction of the hydroalcoholic extract showed affinity for the barbiturate receptor and to some extent for peripheral benzodiazepine receptors. The aqueous total extract A, the aqueous fraction B derived from the hydroalcoholic extracts, as well as the hydroalcoholic extracts demonstrated affinity for GABA-A receptors. This interaction at the receptor level could represent the molecular basis for the sedative effect noted with *Valeriana officinalis* [91].

3.5.1.BJ] Zolpidem

- 1) Interaction Effect: an increase in central nervous system depressant effects
- 2) Summary: The concomitant use of [zolpidem](#) with any central nervous system depressant agent including sedatives (eg, [alprazolam](#), [diazepam](#), or [midazolam](#)) may result in additive CNS depressant effects. Systematic evaluations of [zolpidem](#) in combination with other CNS-active drugs is limited. When administering [zolpidem](#) and a sedative together, dosage adjustments of one or both agents may be necessary [140].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Dosage adjustments may be necessary when [zolpidem](#) is administered with sedative/hypnotic drugs because of the potentially additive effects [140].
- 7) Probable Mechanism: additive effects

3.5.2] Drug-Food Combinations

3.5.2.A] Caffeine

- 1) Interaction Effect: reduced sedative and anxiolytic effects of [flurazepam](#)
- 2) Summary: [Caffeine](#), in a dose-related manner, can counteract benzodiazepine-induced impairment (drowsiness, mental slowness) in some tasks during performance testing. Higher doses (500 mg, equivalent to 4 or more cups of brewed coffee) may interfere with anxiolytic effects, but the clinical significance is uncertain [142] [143] [144].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor benzodiazepine response for desirable outcome. Reduction or elimination of [caffeine](#) exposure would be expected to restore desirable sedative effects (nighttime sedation).
- 7) Probable Mechanism: central nervous system antagonistic effects
- 8) Literature Reports

a) Eighteen normal volunteers were randomly studied after receiving 125, 250, or 500 mg of [caffeine](#), both alone and in combination with [lorazepam](#) 2.5 mg, with each subject serving as his own control. Performance testing included critical flicker fusion, verbal learning, digit-symbol substitution, symbol copying, and number cancellation. [Caffeine](#) significantly improved

performance on the digit-symbol substitution test when given alone and reduced lorazepam-induced impairment during concurrent administration of both agents. In the symbol copying test, [caffeine](#) counteracted the lorazepam-induced impairment. Although normal subjects were used, [lorazepam](#) induced mood changes characterized as withdrawn, tranquil, and less anxious. The highest dose of [caffeine](#) (500 mg) also counteracted the anti-anxiety effects of [lorazepam](#). The study suggests that only moderate doses of [caffeine](#) should be combined with [lorazepam](#). It further raises the question of the potential effects of [caffeine](#) in patients taking benzodiazepines chronically [141].

3.5.2.B] Ethanol

- 1]) Interaction Effect: increased sedation, increased risk of complex behaviors such as "sleep driving"
- 2]) Summary: Concomitant administration of [flurazepam](#) with ethanol may result in additive central nervous system depression, and may increase the risk of complex behaviors such as "sleep-driving." Patients should use caution when motor skills are required as the combination can cause [impairment of psychomotor](#) skills. Due to the presence of psychoactive metabolites, the potential for this interaction may persist for several days after discontinuing [flurazepam](#) [10].
- 3]) Severity: moderate
- 4]) Onset: unspecified
- 5]) Substantiation: theoretical
- 6]) Clinical Management: Patients receiving [flurazepam](#) should use caution if consuming ethanol, due to the risk of additive central nervous system depression, and increased risk of complex adverse events such as "sleep driving" (driving while not fully awake, with amnesia for that time period). Instruct patients to use caution when motor skills are required as the combination can cause [impairment of psychomotor](#) skills. Due to the presence of psychoactive metabolites, the potential for this interaction may persist for several days after discontinuing [flurazepam](#) [10].
- 7]) Probable Mechanism: additive CNS depression

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

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

4.1] Monitoring Parameters

A]) [Flurazepam](#) Hydrochloride

1]) Therapeutic

- a]) Improvement in onset, duration and quality of sleep.

2]) Toxic

- a]) Excessive CNS drowsiness, ie, "hypnotic morning hangover".
- b]) Excessive usage of the drug.

4.2] Patient Instructions

A) Flurazepam (By mouth)

Flurazepam

Treats insomnia (difficulty sleeping). Belongs to the group of drugs called benzodiazepines.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [flurazepam](#) or other medicines that are like [flurazepam](#) (such as [alprazolam](#), [diazepam](#), [temazepam](#), [triazolam](#), [Halcion®](#), [Restoril®](#), [Valium®](#), or [Xanax®](#)).

Do not use this medicine if you are pregnant or planning to become pregnant.

How to Use This Medicine:

Capsule

Your doctor will tell you how much medicine to use. Do not use more than directed. .

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

If a Dose is Missed:

If you forget to use your medicine, use it as soon as you can for sleeping problems. You should not use two doses in the same evening. It may take a full hour (60 minutes) for the medicine to work for sleep.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

It is not safe to take this medicine during pregnancy. It could harm an unborn baby. Tell your doctor right away if you become pregnant.

Make sure your doctor knows if you are breastfeeding, or if you have [kidney disease](#), liver disease, [glaucoma](#), or lung disease.

Older adults may be more sensitive to some of the side effects from this medicine.

This medicine may cause a serious type of [allergic reaction](#) called [anaphylaxis](#). [Anaphylaxis](#) can be life-threatening and requires immediate medical attention. Stop taking this medicine and call your doctor right away if you have itching, hives, trouble with breathing, or any swelling of your hands, face, or mouth when you take this medicine.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also cause sleep-related behaviors, such as driving a car (sleep-driving), walking (sleep-walking), having sex, making phone calls, or preparing and eating food while you are asleep or not fully awake. If these behaviors occur, tell your doctor right away.

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working. If you continue to have problems with sleeping, check with your doctor. Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Chest pain or trouble with breathing.
Depression or severe confusion.
Feeling anxious, nervous, or irritable.
Severe drowsiness and weakness.
Slow, fast, or pounding heartbeat.
Unsteadiness, falling, or having a hard time standing up.
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:

Blurred vision or headache.
Drowsiness, dizziness, clumsiness, or trouble with concentrating.
Dry mouth, nausea, vomiting, diarrhea, constipation, or stomach pain.
Feeling "hangover" the next morning after bedtime use.
Joint or body pain.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) Benzodiazepine hypnotics should always be used in the smallest effective dose for the shortest period of time. Short-acting benzodiazepines are usually preferred for the treatment of insomnia, however, **flurazepam**, a long-acting benzodiazepine, may be appropriate for the nervous/anxious patient requiring next day sedation.

B) **Flurazepam** induces sleep within 15 to 45 minutes and has a significant duration of action to provide a hypnotic effect throughout the night. **Flurazepam's** metabolite, desalkylflurazepam, provides sedation for 10 to 30 hours with relief of daytime anxiety if needed [166]. Sleep may actually be improved on the second and third nights due to the accumulation of the metabolite. Accumulation of the metabolite may also cause harmful adverse effects such as oversedation and impaired daytime functioning.

4.4] Mechanism of Action / Pharmacology

A) REVIEW ARTICLES

1) The use of benzodiazepine derivatives, including their pharmacokinetics, clinical use in anxiety, depression and mixed anxiety depression, sleep disorders, alcohol withdrawal, **musculoskeletal disorders**, **anesthesia** and surgery as well as their adverse drug reactions, have been evaluated [163] [164].

4.5] Therapeutic Uses

4.5.A] **Flurazepam**

4.5.A.1] Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.5.B] **Flurazepam Hydrochloride**

4.5.B.1] **Insomnia**

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (15 y and older)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

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

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

b) Summary:

Effective in inducing sleep and reducing sleep awakenings [1]

Short-term use is recommended

c) Adult:

1) In a double-blind placebo study of 42 patients with 42 controls receiving [FLURAZEPAM](#) 30 milligrams orally at bedtime for 1 night, [FLURAZEPAM](#) induced sleep faster with a longer duration of sleep. Patients were reported to be more refreshed and alert upon awakening compared to placebo. In the crossover study, 66% of the patient population preferred the active medication, 7% preferred the placebo, and 27% had no preference. One patient complained of hangover effect and 1 patient complained of restlessness. Two patients complained of nightmares although it was possible that this was unrelated to the drug. Nervousness and headache were reported in 1 patient each on placebo and 2 patients on placebo noted nightmares [2].

2) In a study of 12 patients receiving [FLURAZEPAM](#) 30 milligrams at bedtime for 4 days compared with 4 patients on placebo, [FLURAZEPAM](#) was effective in reducing sleep latency, wake time after sleep onset, total wake time, and number of wakes from base line. Patients on placebo were reported to have all of those parameters increased above mean values but were noted to be below baseline [3].

3) [FLURAZEPAM](#) in doses of 30 milligrams at bedtime was demonstrated to be significantly more effective than placebo in producing greater total sleep time, fewer awakenings, and less total awake time in postoperative [herniorrhaphy](#) patients [4].

4.6] Comparative Efficacy / Evaluation With Other Therapies**4.6.A] [Amobarbital](#)****4.6.A.1] Insomnia**

a) [Flurazepam](#) 15 milligrams and [amobarbital](#) 50 milligrams were both effective in inducing sleep in 27 patients in a cross-over study. No significant differences were noted in side effects [175]. In a similar study, [amobarbital](#) 100 milligrams plus [secobarbital](#) 100 milligrams ([Tuinal\(R\)](#)) was superior to [flurazepam](#) 30 milligrams in inducing and maintaining sleep. Effects persisted beyond the fourteenth night of treatment, suggesting that tolerance did not develop to the hypnotic effect. No significant [psychomotor impairment](#) was noted with drug usage [176].

4.6.B] [Brotizolam](#)**4.6.B.1] Insomnia**

a) Brotizolam 0.25 to 0.5 milligram nightly has been at least as effective as flurazepam 15 to 30 milligrams nightly in the treatment of insomnia in comparative controlled studies [177] [178]. One study suggested the superiority of brotizolam, however, statistical comparisons were not provided (Sanchez-Martinez & Landa Palos, 1982).

b) The effects of 0.25 milligram of brotizolam, flurazepam 15 milligrams, and placebo on sleep and performance were compared in 36 elderly subjects with chronic insomnia during a 2-week period of administration [179]. Sleep improved with all treatments. Rebound insomnia was noted on brotizolam withdrawal; flurazepam withdrawal had a milder impact. Both drug treatments increased daytime sleepiness and impaired performance on the first day after their administration. These effects waned after 2 weeks of treatment with brotizolam but not flurazepam. The results of this study affirm the increased sensitivity of elderly subjects to benzodiazepine hypnotics and their indication for acute or intermittent insomnia, rather than for the more chronic forms of this disorder.

4.6.C] Doxylamine

4.6.C.1] Insomnia

a) No statistically significant difference was found between doxylamine succinate and flurazepam in the average time required for 200 patients with mild-to-moderate insomnia to fall asleep over 5 nights following a nightly dose of doxylamine succinate 25 milligrams or flurazepam 30 milligrams, nor was any statistically significant difference found in the total time the 200 patients slept. Patients on doxylamine awoke an average of 1.2 times per night while those on flurazepam awoke an average of 0.9 times per night. On a rating scale of 1 to 5, doxylamine was given a 3, flurazepam a 3.4 by patients rating the degree of restfulness (5 represents "very well rested"). Although statistically significant, the difference between doxylamine 25 mg and flurazepam 30 mg in the number of awakenings and degree of restfulness are clinically insignificant (Prod Info Unisom(R), 1997).

4.6.D] Estazolam

4.6.D.1] Insomnia

a) Estazolam was shown to be as effective as flurazepam in a multicenter, placebo-controlled study of 230 patients with chronic insomnia. Patients were randomized to receive either estazolam 2 milligrams, flurazepam 30 milligrams, or placebo each night at bedtime for 7 consecutive nights. All parameters measured by the investigators' global evaluations improved significantly more with either estazolam (p less than 0.05) or flurazepam (p less than 0.001) than with placebo. Estazolam was rated as being comparable to flurazepam for all parameters except depth of sleep, for which flurazepam was found to be significantly better (p less than 0.05). A marked or moderate improvement in sleep was reported by 81%, 78%, and 36% of patients receiving estazolam, flurazepam, or placebo, respectively. The percentage of patients reporting adverse experience was greatest for flurazepam (72%), followed by estazolam (59%), and placebo (43%). The authors felt that estazolam 2 milligrams was as effective as flurazepam 30 milligrams over the 7-day study period, and was better tolerated [167].

b) Estazolam, in 1 or 2 milligram doses, was as effective as 30 milligrams of flurazepam in improving the quality of sleep, decreasing the number of awakenings, and also equally effective in increasing sleep duration, total sleep time, and depth of sleep in 223 insomniac outpatients. Estazolam 2 mg, but not 1 mg, was as effective as flurazepam 30 mg in reducing sleep latency. Both drugs significantly improved all of the above sleep parameters when compared with placebo. A high incidence of mild to moderate adverse drug experiences were reported in all groups: flurazepam 30 mg, 68%; estazolam (2 mg), 58%; estazolam (1 mg), 54%, and placebo 43% [168].

4.6.D.2) Adverse Effects

a) Neither [estazolam](#) 2 milligrams or [flurazepam](#) 30 milligrams caused any clinical signs of [respiratory depression](#) during the awake state or during sleep in a double-blind, placebo-controlled, crossover study in 29 patients with mild COPD (mean age 48 years) [169]. [Estazolam](#), [flurazepam](#), and placebo were each administered for 5 days followed by a 2-week washout period. The only significant difference between placebo and [estazolam](#) was in the pre-ejection period for systolic time interval ($p=0.038$). Statistically significant differences between placebo and [flurazepam](#) were seen in increased respiratory frequency and heart rate, and decreases in [oxygen saturation](#), inspiratory time, and systolic blood pressure. However, clinical signs of [respiratory depression](#) were not seen in any patient.

b) Adverse reactions were significantly more common and more severe with [flurazepam](#) 30 milligrams ($n=24$) than with [estazolam](#) 2 milligrams ($n=20$) in a double-blind, placebo-controlled study in 65 insomniac outpatients [170]. Residual daytime drowsiness and fatigue accounted for 73% of all side effects with both active drugs. Fifty percent of [estazolam](#)-treated patients reported no adverse effects compared with only 17% of [flurazepam](#)-treated patients (p less than 0.05). Although both drugs were rated on a global evaluation as significantly better than placebo, [estazolam](#) was significantly better than [flurazepam](#) in only 1 of 6 measures of efficacy (quality of sleep). There was no difference in the two treatment groups in overall improvement of sleep.

4.6.E] Loprazolam

4.6.E.1] Insomnia

a) Loprazolam 0.5 and 1 milligram (mg) and [flurazepam](#) 15 mg were equally effective in all sleep parameters. Loprazolam at 2 mg was significantly more effective in hypnotic measures, but was also associated with more adverse effects, notably morning hangover [171].

b) Loprazolam 1 milligram (mg) and [flurazepam](#) 15 mg were equally effective in a placebo-controlled, double-blind, multicenter study of 264 insomniac patients. Both drugs were statistically superior to placebo. Loprazolam demonstrated less headache and hangover (residual effects on balance) than [flurazepam](#) [172].

4.6.F] Lorazepam

4.6.F.1] Insomnia

a) A double-blind, placebo-controlled, crossover study involving 15 patients and 15 controls compared oral [lorazepam](#) 2 to 4 milligrams as a single dose with [flurazepam](#) in the treatment of insomnia [173]. Results indicated that [lorazepam](#) in a dose of 2 to 4 mg was significantly superior to placebo and [flurazepam](#) 15 milligrams based on onset, duration, depth of sleep, frequency of awakening, and subjective satisfaction. However, the 2 and 4 mg dose of [lorazepam](#) was equivalent to [flurazepam](#) 30 mg. There appeared to be no significant difference between the 2 and 4 mg doses of [lorazepam](#).

b) Hypnotic efficacy and safety of 3 weeks of daily doses of 2 milligrams [lorazepam](#) or 30 milligrams [flurazepam](#) were compared in a double-blind crossover study in 8 chronic insomniacs [174]. Subjects were monitored in the sleep laboratory twice weekly for a total of 25 nights. Subjective estimates of sleep, vigilance tests, and adverse effects were recorded throughout the study. It was found that neither drug impaired REM sleep or vigilance test performance. Side effects of grogginess were expected. Both [lorazepam](#) 2 mg and [flurazepam](#) 30 mg were found to be effective and safe. [Lorazepam](#) had more favorable effects on sleep than did [flurazepam](#).

4.6.G] Lormetazepam

4.6.G.1] Insomnia

a) Comparisons between lormetazepam and flurazepam in the treatment of insomnia have demonstrated comparable efficacy between the agents. Any differences in the side effect profiles of these agents could be attributed to the differing pharmacokinetics. Lormetazepam at doses ranging from 1 to 2.5 milligrams has been compared to flurazepam 30 milligrams in studies varying in duration from 1 to 3 weeks in both young patients, mean age 30 years, and elderly patients, mean age 61 years. Results have consistently demonstrated equal efficacy and have shown good tolerability of lormetazepam [213] [214] [215].

4.6.H] Midazolam

4.6.H.1] Administration of medication - Preoperative care

a) Rectally administered midazolam, in doses of 0.3 milligrams per kilogram (mg/kg), was found to be comparably effective to 5 mg/kg of ketamine rectally for preanesthetic medication for dental extractions in sixty children [212]. Midazolam appeared marginally but not significantly more efficacious than ketamine.

4.6.H.2] Insomnia

a) Midazolam and flurazepam 15 and 30 milligrams (mg) were comparable in efficacy in a multicenter, placebo-controlled, 14-day study in 99 chronic insomniacs (25 to 57 years of age) [208]. The subjects were divided into 4 treatment groups: midazolam 15 mg, flurazepam 15 mg and 30 mg, and placebo. Compared with placebo, all 3 drug treatments significantly improved sleep during nights 1 and 2, but none of them showed significant improvement on nights 7, 13, or 14. However, significant improvement was seen in all 3 treatment groups throughout the study period when compared to baseline rather than the placebo treatment.

4.6.H.3) Adverse Effects

a) Midazolam and flurazepam 15 milligrams (mg) were comparable with respect to adverse effects in a multicenter, placebo-controlled, 14-day study in 99 chronic insomniacs (25 to 57 years of age). The subjects were divided into 4 treatment groups: midazolam 15 mg, flurazepam 15 and 30 mg, and placebo. There were no significant differences between midazolam and flurazepam with respect to patient tolerance; there was no adverse effect on any organ system [209]. Flurazepam 30 mg impaired next-day cognitive performance as measured by reading comprehension, addition, and a digital symbol substitution test. Neither midazolam or the low-dose flurazepam resulted in any impairment [210]. Midazolam caused no overall impairment of psychomotor tasks, flurazepam 30 mg resulted in impairment at some point throughout the study, and flurazepam 15 mg resulted in some impairment compared with baseline, but the impairment was not as great as with the higher flurazepam dose [211].

4.6.I] Nitrazepam

4.6.I.1] Insomnia

a) SUMMARY: Studies to date have not demonstrated any significant advantage of nitrazepam over flurazepam for the treatment of insomnia. Controlled studies in larger numbers of patients will be required to more completely evaluate any advantages nitrazepam may have over flurazepam.

b) Nitrazepam 5 milligrams daily was compared with flurazepam 15 milligrams and fosazepam 60 mg daily in a double-blind, crossover study in 17 psychogeriatric patients in a 5-week trial [217]. All drugs were considered equivalent in their ability to maintain sleep; however, side effects on motor and mental performance were greater in patients receiving nitrazepam. Rebound-insomnia on the first night following drug withdrawal was also more significant with nitrazepam.

c) The hypnotic effects of nitrazepam were compared with flurazepam in 9 healthy volunteers using 24-hour polygraphy [218]. Flurazepam 15 milligrams was reported to be a more effective hypnotic agent, but may have greater residual effects on the following day. Flurazepam was more effective in prolonging sleep time, shortening sleep latency, decreasing the waking period, and increasing the percentage of stage II sleep than nitrazepam.

4.6.J] Oxazepam

4.6.J.1] Insomnia

a) Oxazepam was as effective for inducing sleep in insomniacs as flurazepam. Fourteen patients with chronic insomnia were randomly administered either flurazepam 30 milligrams or oxazepam 30 milligrams. Both agents improved sleep as assayed by polysomnographic evaluation, but flurazepam induced daytime sleepiness and oxazepam did not [216].

4.6.K] Quazepam

4.6.K.1] Insomnia

a) Both flurazepam and quazepam are considered long-acting benzodiazepine hypnotics, and both have demonstrated long-term effectiveness as well as "carryover effectiveness" on the first 2 to 3 nights. Neither drug is likely to induce rebound insomnia, even during extended withdrawal periods [180] [181] [182] [183]. Both drugs may impair performance on the day after their use ("hangover effects") [184] [182] [183]. Hangover effects have been more frequent and severe with quazepam 30 milligrams at bedtime than flurazepam 30 milligrams at bedtime, which is most likely related to the accumulation of 3 compounds with long half-lives following quazepam administration (quazepam, 2-oxoquazepam, N-desalkyl-2-oxoquazepam) [183]. However, this effect is not necessarily related to kinetic properties of quazepam and flurazepam, since hangover effects appear more intense during the first several days of use rather than during long-term administration [183] [185]. In addition, hangover effects are not unique to the long-acting benzodiazepines [186] [183].

b) The efficacy and side effects of quazepam 15 and 30 milligrams and flurazepam 30 milligrams were compared in the short-term (3 days), intermediate-term (2 weeks) and long-term (4 weeks) treatment of insomnia in 18 subjects (22 to 60 years of age) [183]. Quazepam 15 and 30 mg and flurazepam 30 mg were all effective in sleep induction and maintenance of sleep after short- intermediate-term use, and both drugs were similarly effective, although strict comparisons of efficacy were not emphasized. With long-term administration (4 weeks), both drugs remained effective, although some loss of efficacy was observed; however, flurazepam was more effective than either dose of quazepam during long-term treatment. Rebound insomnia following abrupt withdrawal was not observed with either drug during 15 days of observation. Carryover effectiveness was seen in the first 2 to 3 nights following withdrawal, with quazepam 30 mg producing much greater carryover effectiveness than flurazepam 30 mg. Quazepam 30 mg produced more side effects (hangover effects) than flurazepam 30 mg, both with regard to frequency and severity; quazepam 15 mg produced only minimal daytime sedation. Differences in hangover effects were attributed to the cumulative effects of quazepam plus its metabolites, each with long half-lives, as compared to accumulation of only one active metabolite of flurazepam. The difference in side effects (hangover sedation) between 15 and 30 mg doses of quazepam was attributed to the dose-related nature of side effects of quazepam.

c) Based upon these data, it appears that optimal doses of both quazepam and flurazepam for insomnia are 15 milligrams at bedtime, which produce fewer side effects than 30 mg doses. With regard to comparative efficacy, flurazepam would appear to be a more rational choice over quazepam for the long-term treatment of insomnia, due to its superior efficacy during long-term administration and a lower incidence of side effects when compared with equivalent doses of quazepam.

d) Two randomized, parallel, and double-blind studies in insomniacs concluded that [quazepam](#) 15 milligrams produces less daytime somnolence and fewer psychomotor performance decrements than does [flurazepam](#). Performance test results suggested [quazepam](#) has a relatively low potential for daytime impairment [187].

4.6.L] [Secobarbital](#)

4.6.L.1] [Insomnia](#)

a) During a one-week study comparing the effects of [secobarbital](#) 100 milligrams, [flurazepam](#) 30 milligrams, L-tryptophan 1 g, and placebo on sleep in 96 insomniacs, [flurazepam](#) produced significant improvement on several sleep measures compared with placebo, while [secobarbital](#) and L-tryptophan did not. A randomized, double-blind study was conducted in 96 patients complaining of insomnia for at least 6 months [204]. Each patient was asked to rate sleep parameters and mood each morning during the 7-day treatment period and the 7-day follow-up period on standardized questionnaires. [Flurazepam](#) was the only treatment which produced significant 'beneficial' effects on 3 measures: estimates of 'how well slept' and 'how felt in the morning' were better than placebo during the treatment week, and the 'global outcome' (how well the patient felt the treatment medication helped their insomnia) was higher at the final rating. Neither [secobarbital](#) nor L-tryptophan proved significantly better than placebo during the treatment period. [Flurazepam](#) and [secobarbital](#) produced withdrawal symptoms during the post-treatment week, while L-tryptophan and placebo did not.

4.6.M] [Temazepam](#)

4.6.M.1] [Insomnia](#)

a) The efficacy and safety of [temazepam](#) 30 milligrams and [flurazepam](#) 30 milligrams were similar in a double-blind study of 75 geriatric patients with insomnia [205]. There was less drug hangover with [temazepam](#) than with [flurazepam](#) due to the shorter half-life of [temazepam](#). Also, [flurazepam](#) has a long-acting metabolite while [temazepam](#) has no active metabolites.

b) [Temazepam](#) was as effective as [flurazepam](#) for inducing sleep but did not cause performance problems the day after therapy. Twenty-four healthy subjects (12 men and 12 women) were administered [flurazepam](#) 30 milligrams, [temazepam](#) 40 milligrams, and then placebo. Subjectively, [flurazepam](#) induced more satisfactory sleep than [temazepam](#), but 3 mental function tests demonstrated [temazepam](#) caused less impairment than [flurazepam](#) [206].

c) Both [temazepam](#) and [triazolam](#) induced maximum sedative effects that corresponded to maximum plasma levels in a single-dose, placebo-controlled, double-blind study in 52 healthy subjects. [Triazolam](#) 0.25 mg induced greater sedation than [temazepam](#) 15 milligrams, but both agents were more sedative than [flurazepam](#) 15 milligrams. Recovery corresponded in all agents to elimination half-life, although sedative effects were abolished prior to plasma elimination. Sedative effects were greatest for [triazolam](#) followed by [temazepam](#), with [flurazepam](#) being similar to placebo [207].

4.6.N] [Triazolam](#)

4.6.N.1] [Insomnia](#)

a) SUMMARY: [Triazolam](#) appears to be equal in efficacy to [flurazepam](#), although some studies claim that [triazolam](#) is superior. Comparison of studies is made difficult by variations in study design and duration, drug dosage, and patient population.

b) After a 2-week period of receiving nightly single-blind placebo, patients (65 years or older) were randomly given either [triazolam](#) (0.125 milligram) or [flurazepam](#) (15 milligrams) nightly under double-blind conditions. Triazolam-treated patients were found to have subsequent improvement on psychomotor

tests, whereas flurazepam recipients showed performance impairment during treatment. The findings suggest that the kinetic differences between flurazepam and triazolam may have clinical implications in elderly patients undergoing rehabilitation therapy [189].

c) In long-term sleep studies (7 to 21 days of therapy) the reduction in sleep latency with comparable doses of triazolam and flurazepam was not considered significantly different [190] [191]. In these reports, the total sleep time, number of awakenings, and sleep quality were also not significantly different between the two agents. Triazolam, with a shorter half-life, results in a lower incidence of hangover effects and daytime sedation than flurazepam during the first few days of administration; however, differences in morning sleepiness with flurazepam and triazolam generally disappear after a few days of treatment [192]. Several studies have demonstrated that decrements in performance measured the day after hypnotic doses are similar for all hypnotic agents [192] [193] [194] [195] [196]. Some data indicate that plasma levels of benzodiazepines do not clearly explain effects of the drug on performance the day after, as evidenced by a lower incidence of performance decrements with nitrazepam 10 milligrams as compared with flurazepam 30 milligrams in one report [194]. Morning hangover effects appear to be related more to the benzodiazepine dose than to plasma half-life (Johnson & Cheraik, 1982). Doubling the dose of triazolam from 0.5 to 1 milligram is the equivalent of doubling a 30 mg dose of flurazepam to 60 mg, resulting in marked daytime drowsiness. Higher doses of triazolam (1 to 1.5 mg) would be expected to produce more morning hangover than flurazepam [192].

d) Both triazolam 0.5 milligrams and flurazepam 30 milligrams produced similar hangover effects, impairment of motor performance, and increased sleepiness on the morning following bedtime administration [197].

e) Triazolam was superior to flurazepam in a placebo-controlled study of hypnotic effects in geriatric patients with insomnia [198]. Fourteen patients (age 63 to 78 years) received oral triazolam 0.25 milligram at bedtime for 28 days. Fourteen patients served as placebo controls and 13 patients received flurazepam. Triazolam was shown to be significantly superior to placebo in sleep parameters which included onset of sleep, duration of sleep, quality of sleep, and number of awakenings during the night. Triazolam was superior to flurazepam on duration of sleep and was rated higher, but not significantly, on the other variables. Over the 28 day period no tolerance developed. Triazolam was superior to flurazepam in geriatric patients [199].

f) In a study of triazolam and flurazepam using daytime sleepiness as a criterion in Hypnotic Medication Trials, flurazepam significantly decreased median sleep latency (ie, increased daytime sleepiness) whereas triazolam had no effect [200]. When subjects were subdivided by basal levels of daytime sleepiness, based on the median of the 24 baseline sleep latency measures, flurazepam tended to increase sleepiness regardless of this basal sleepiness. In the sleepiest subjects, however, triazolam showed a nonsignificant tendency to make subjects more alert.

g) Both flurazepam and triazolam should be equally effective when given for more than one day. Adverse effects of each drug, including morning sedation, are clearly more dose related than half-life related. Occasional use of benzodiazepines for insomnia would favor the use of triazolam in patients who want to fall asleep quickly, who do not go to bed until midnight or later and have to get up early the next morning. In these patients, the lowest possible dose of triazolam is indicated. In insomniac patients who also have a component of tenseness and anxiety or increased psychic distress, the occasional use of flurazepam, which can result in higher incidence of daytime sedation, might be desirable [201] [192]. For the long-term treatment of insomnia, there would not appear to be a significant difference between triazolam or flurazepam [192] [191] [202].

4.6.N.2) Efficacy

a) Fifty-two healthy adult male and female volunteers received single oral doses of flurazepam 15 milligrams, temazepam 15 milligrams, triazolam 0.25 milligram, or placebo in a parallel, double-blind study. Maximum sedative effects of triazolam and temazepam corresponded closely with the time to reach C_{max}. Sedation associated with triazolam had a rapid onset but was comparable to placebo at

three hours after dosing. The amnestic effect of triazolam was quantitatively greater than the other two hypnotics [203].

4.6.O] Tryptophan

4.6.O.1] Insomnia

a) One study reported that flurazepam 30 milligrams at bedtime was more effective than tryptophan 1 gram at bedtime or secobarbital 100 milligrams at bedtime in severe insomniac patients for a period of 7 nights [188].

4.6.P] Zaleplon

1) Adverse Effects

a) Next-day sedation was observed with flurazepam 30 milligrams (mg) but not zaleplon 10 or 20 mg in a placebo-controlled study [220]. Patients (n=93) received either zaleplon or flurazepam and were evaluated the next day with multiple sleep latency tests. Next-day sedation was not significantly different from placebo with either the zaleplon 10-mg or 20-mg doses. Flurazepam 30 mg produced significantly more next-day sedation than placebo and both zaleplon doses (all tests, p less than 0.001).

4.6.Q] Zopiclone

4.6.Q.1] Preoperative sedation

a) When administered the night before surgery as a preoperative hypnotic, zopiclone 7.5 milligrams has been reported less effective than flurazepam 30 milligrams and flunitrazepam 2 milligrams. Zopiclone 7.5 or 10 milligrams has been comparable to nitrazepam 5 or 10 milligrams in this setting [219].

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