

DRUGDEX-EV 2385

MICROMEDEX

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CLORAZEPATE

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0.0] Overview

1] Class

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

Antianxiety
Anticonvulsant

2] Dosing Information

a) [Clorazepate](#) Dipotassium

1] Adult

a) [Alcohol withdrawal syndrome](#)

1) Day 1: initial, 30 mg immediate-release ORALLY; then 30 to 60 mg ORALLY for the remainder of the day in divided doses; MAX, 90 mg/day [1] [2]

2) Day 2: 45 to 90 mg/day ORALLY in divided doses; MAX, 90 mg/day [1] [2]

3) Day 3: 22.5 to 45 mg/day ORALLY in divided doses [1] [2]

4) Day 4: 15 to 30 mg/day ORALLY in divided doses; avoid excessive reductions on successive days [1] [2]

5) Day 5 and after: 7.5 to 15 mg/day ORALLY in divided doses until the patient's condition is stable; avoid excessive reductions on successive days [1] [2]

b) Anxiety

1) immediate release, 15 to 60 mg/day ORALLY in divided doses; usual dose is 30 mg/day (in divided doses), OR alternatively initial, 15 mg at bedtime, titrated to clinical effect [1]

2)) sustained-release, 11.25 to 22.5 mg ORALLY as single dose every 24 hours; the 22.5 mg tablet is intended as an alternative dosage form for patients stabilized on a dose of 7.5 mg 3 times daily; the 11.25 mg tablet is intended as an alternative dosage form for patients stabilized on a dose of 3.75 mg 3 times daily; sustained-release formulation should not be used to initiate clorazepate therapy [2]

c)) Partial seizure; Adjunct

1)) initial, 7.5 mg ORALLY 3 times a day [1] [2]

2)) maintenance, may increase dose by 7.5 mg/wk to a MAX of 90 mg/day ORALLY (divided doses) [1] [2]

2)) Pediatric

a)) use not recommended in children under age 9 yr [2]

1)) Partial seizure; Adjunct

a)) (9 to 12 yr) initial, 7.5 mg ORALLY 2 times a day [1] [2]

b)) (9 to 12 yr) maintenance, may increase dose by 7.5 mg/wk to a MAX of 60 mg/day ORALLY (divided doses) [1] [2]

c)) (over 12 yr) initial, 7.5 mg ORALLY 3 times a day [1] [2]

d)) (over 12 yr) maintenance, may increase dose by 7.5 mg/wk to a MAX of 90 mg/day ORALLY (divided doses) [1] [2]

3)) Contraindications

a)) [Clorazepate](#) Dipotassium

1)) acute [narrow angle glaucoma](#) [1]

2)) hypersensitivity to [clorazepate](#) [1]

4)) Clinical Applications

a)) [Clorazepate](#) Dipotassium

1)) FDA Approved Indications

a)) [Alcohol withdrawal syndrome](#)

b)) Anxiety

c)) Partial seizure; Adjunct

1.0] Dosing Information

[Drug Properties](#)
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1.1] Drug Properties

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

B)] Synonyms

[Clorazepate](#)
[Clorazepate](#) Dipotassium
[Clorazepate](#) Potassium
Clorazepic Acid

C)] Physicochemical Properties

1)] [Clorazepate](#) Dipotassium

a)] Molecular Weight

1)] 408.92 [40]

b)] Solubility

1)] Very soluble in water and insoluble in the common organic solvents [40].

1.2] Storage and Stability

A)] [Clorazepate](#) Dipotassium

1)] Oral route

a)] Tablet

1)] Store at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F). Protect from light and moisture [40].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] [Clorazepate](#) Dipotassium

1.3.1.A.1] Oral route

1.3.1.A.1.a] [Alcohol withdrawal syndrome](#)

1)) The following schedule is recommended for the symptomatic relief of acute alcohol withdrawal [1] [2]:

First 24 hours (Day 1)

Clorazepate 30 milligrams, initially; followed by 15 milligrams in divided doses

Second 24 hours (Day 2)

Clorazepate 45 to 90 milligrams in divided doses

Third 24 hours (Day 3)

Clorazepate 22.5 to 45 milligrams in divided doses

Fourth 24 hours (Day 4)

Clorazepate 15 to 30 milligrams in divided doses

Thereafter, the dose should be gradually reduced to 7.5 to 15 milligrams/day. Drug therapy should be discontinued as soon as the patient is stable

2)) The maximum daily clorazepate dose is 90 milligrams. Avoid excessive reductions in the total amount of drug administered on successive days [1] [2].

1.3.1.A.1.b) Anxiety

1)) Immediate Release

a)) The recommended dose for the treatment of anxiety is clorazepate 30 milligrams (mg)/day orally in divided doses. The dose should be adjusted gradually within the range of 15 to 60 mg/day orally in divided doses, according to patient response. Alternatively clorazepate may also be administered as a single bedtime dose. The usual recommended dose is 15 mg, which should then be adjusted according to patient response [1].

b)) A number of studies indicate that administration of clorazepate in a single daily dose preferably at bedtime is as effective and safe as administering the drug in divided doses or administering diazepam in divided doses [20] [21].

2)) Sustained Release

a)) The sustained-release formulation of clorazepate is administered as a single dose every 24 hours. The 22.5 milligram (mg) tablet is intended as an alternative dosage form for patients stabilized on a dose of 7.5 mg 3 times daily. The 11.25 mg tablet is intended as an alternative dosage form for patients stabilized on a dose of 3.75 mg 3 times daily. The sustained-release formulation should not be used to initiate clorazepate therapy [2].

1.3.1.A.1.c) Partial seizure; Adjunct

1)) When using clorazepate as an adjunct to antiepileptic drugs, the maximum recommended initial dose in patients over 12 years of age is 7.5 milligrams orally 3 times daily. The dosage should be increased by no more than 7.5 milligrams every week and should not exceed 90 milligrams/day. In order to minimize drowsiness, the recommended initial dose and dosage increments should not be exceeded [1] [2].

1.3.2] Dosage in Renal Failure

A) Clorazepate Dipotassium

1)) No dosage adjustments are required for patients with renal failure [33].

1.3.3] Dosage in Hepatic Insufficiency

A) Clorazepate Dipotassium

1j) Among the class as a whole, [lorazepam](#), [oxazepam](#), and [temazepam](#) may be the benzodiazepines of choice for patients with liver disease. These 3 agents undergo glucuronide conjugation and their half-lives are only slightly altered in the presence of [hepatic dysfunction](#). Other benzodiazepines may be used, but the dosage or dosing interval may need to be altered to compensate for impaired hepatic metabolism [34] [35] [36] [37] [38] [39].

1.3.4] Dosage in Geriatric Patients

A) [Clorazepate](#) Dipotassium

1j) The recommended starting dose of clorazepate among the elderly or debilitated patients is 7.5 to 15 mg [1].

2j) In elderly patients the initial dose should be small and increments should be made slowly and cautiously based on clinical response to avoid ataxia or excessive sedation [1] [2].

1.3.6] Dosage in Other Disease States

A) [Clorazepate](#) Dipotassium

1j) Debilitated

a) In debilitated patients the initial dose should be small (immediate-release 7.5 to 15 mg) and increments should be made slowly and cautiously based on clinical response to avoid ataxia or excessive sedation [1] [2].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] [Clorazepate](#) Dipotassium

1.4.1.A.1] Oral route

1.4.1.A.1.a] Partial seizure; Adjunct

1j) In children 9 to 12 years of age the maximum recommended initial dose as an adjunct to antiepileptic drugs is [clorazepate](#) 7.5 milligrams (mg) orally twice daily. The dose should be increased by no more than 7.5 milligrams every week and should not exceed 60 milligrams/day. In order to minimize drowsiness, the recommended initial dose and dosage increments should not be exceeded [1] [2].

2j) In children over 12 years of age the maximum recommended initial dose as an adjunct to antiepileptic drugs is [clorazepate](#) 7.5 milligrams (mg) orally 3 times a day. The dose should be increased by no more than 7.5 mg every week and should not exceed 90 mg/day. In order to minimize drowsiness, the recommended initial dose and dosage increments should not be exceeded [1] [2].

1.4.1.A.2j) Use is not recommended in children under 9 years of age [2].

1.4.2] Dosage in [Renal Failure](#)

A) [Clorazepate](#) Dipotassium

- 1)) No dosage adjustments are required for patients with renal failure [33].

2.0] Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1] Onset and Duration

A)) Onset

1)) Clorazepate Dipotassium

a)) Peak Response

- 1)) 1 to 2.5 hours [196].

B)) Duration

1)) Clorazepate Dipotassium

a)) Single Dose

- 1)) less than 6 hours [196].

2.2] Drug Concentration Levels

A)) Clorazepate Dipotassium

1)) Time to Peak Concentration

- a)) 0.7 to 1.5 hours [197] [198]

2.3] ADME

2.3.1] Absorption

A)) Clorazepate Dipotassium

1)) Bioavailability

- a)) IM: 100% [199]

- b)) Oral: 91% [197].

2.3.2] Distribution

A)) Distribution Sites

1)) Clorazepate Dipotassium

a) Protein Binding

1) 97% to 98% [40].

a) The protein binding of nordiazepam (primary metabolite) is 97% to 98% [40].

B) Distribution Kinetics**1) Clorazepate Dipotassium****a) Volume of Distribution**

1) 1.05 to 1.54 L/kg [198].

a) An increase in Vd for total desmethyldiazepam was seen with age in both males and females: young males, 1.05 L/kg; elderly males, 1.24 L/kg; young females, 1.28 L/kg; elderly females, 1.54 L/kg [198].

2) Obese patients, 0.94 L/kg [200]

a) The Vd is significantly greater in obese subjects as compared with control (1.52 vs 0.94 L/kg) [200].

2.3.3] Metabolism**A) Metabolism Sites and Kinetics****1) Clorazepate Dipotassium**

a) Liver: extensive [40].

1) Clorazepate dipotassium is metabolized primarily in the liver [40].

B) Metabolites**1) Clorazepate Dipotassium**

a) Nordiazepam: active [201].

1) After oral administration clorazepate dipotassium is rapidly converted to nordiazepam. [40].

b) 3-hydroxynordiazepam: inactive [40]

1) Nordiazepam is hydroxylated to the primary urinary metabolite, 3-hydroxynordiazepam [40].

2.3.4] Excretion**A) Kidney****1) Clorazepate** Dipotassium**a) Renal Clearance (rate)**

1) 0.15 to 0.27 mL/min/kg [198].

b) Renal Excretion (%)

1) 62% to 67% [40].

a) In a pharmacokinetic study (n=2), 62% to 67% of the radiolabeled dose was excreted in the urine within 10 days of administration of a single-dose of clorazepate dipotassium 15 mg orally. On day 10, 1% of the radiolabeled dose was excreted in the urine [40].

B) Feces**1) Clorazepate** Dipotassium

a) 15% to 19% [40].

1) In a pharmacokinetic study (n=2), 15% to 19% of the radiolabeled dose was excreted in the feces within 10 days of administration of a single-dose of clorazepate dipotassium 15 mg orally [40].

2.3.5] Elimination Half-life**A) Parent Compound****1) Clorazepate** Dipotassium

a) 2.29 hours [202].

B) Metabolites**1) Clorazepate** Dipotassium

a) Nordiazepam, approximately 2 days [40].

1) The elimination half-life of nordiazepam (primary active metabolite of chlorazepate dipotassium) is about 2 days [40].

b) Desmethyldiazepam, 46 hours [202].

1) Desmethyldiazepam, elderly: 71.6 to 120.1 hr [198]

a) The mean elimination half-life of desmethyldiazepam is not significantly different for young and elderly females (83.2 hr and 71.6 hr, respectively), but it is significantly longer in elderly males as compared with young males (120.1 hr vs 64 hr) [198].

c) Desmethyldiazepam, Smokers: 29.8 hr [203].

1) The mean elimination half-life is significantly longer in nonsmokers compared with smokers (54.7 hr versus 29.8 hr) [203].

3.0] Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1] Contraindications

A) [Clorazepate](#) Dipotassium

- 1) acute [narrow angle glaucoma](#) [1]
- 2) hypersensitivity to [clorazepate](#) [1]

3.2] Precautions

A) [Clorazepate](#) Dipotassium

- 1) abrupt discontinuation should be avoided due to the potential for withdrawal symptoms [1]
- 2) concomitant use with alcohol; effects of alcohol may be increased [1]
- 3) concomitant use with other CNS depressants should be avoided [1]
- 4) [depressive neuroses](#) or [psychotic reactions](#); not approved for this use [1]
- 5) drug dependence, history of; abuse potential [1]
- 6) elderly or debilitated patients; may require smaller initial dose and increases in gradual increments to preclude ataxia or excessive sedation [1]
- 7) hazardous occupations, such as operating dangerous machinery or motor vehicles; drug may interfere with psychomotor performance [1]
- 8) pediatric patients (younger than 9 years); use not recommended
- 9) pregnancy; may increase risk of [congenital malformations](#); use should be avoided [1]
- 10) prolonged use; monitoring recommended [1]

11)] suicidality, increased risk of, particularly in patients with depression; monitoring recommended; least amount of drug feasible should be prescribed [1]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Clorazepate Dipotassium

3.3.1.A.1] Decreased systolic arterial pressure

a)] A reduction in systolic blood pressure has been reported with [clorazepate](#) use [40].

3.3.2] Dermatologic Effects

3.3.2.A] Clorazepate Dipotassium

3.3.2.A.1] Photoonycholysis

a)] A case of clorazepate-induced [photo-onycholysis](#) was reported. A 36-year-old woman with a history of [alopecia areata](#) was treated for stress with [clorazepate](#) 10 mg/day for several weeks. Pain in all her fingernails developed after she sunbathed for a prolonged time; by the next day, distal [onycholysis](#) and mild [subungual hemorrhage](#) was present in all the nails, and central [onycholysis](#) was seen in some of the nails. Resolution of [onycholysis](#) occurred within 4 months [46].

3.3.2.A.2] Rash

a)] Transient skin rashes have been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- [ACUTE PORPHYRIAS](#)

3.3.4] Gastrointestinal Effects

3.3.4.A] Clorazepate Dipotassium

3.3.4.A.1] Gastrointestinal tract drug side effect

a)] Various gastrointestinal complaints have been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.4.A.2] Xerostomia

a)] Dry mouth has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.5] Hematologic Effects

3.3.5.A] Clorazepate Dipotassium

3.3.5.A.1] Decreased hematocrit level

a)] Decrease in hematocrit has been reported with [clorazepate](#) dipotassium therapy [40].

3.3.6] Hepatic Effects

3.3.6.A] Clorazepate Dipotassium

3.3.6.A.1] Liver function tests abnormal

a) **Abnormal liver function** tests have been reported in patients who received **clorazepate** dipotassium [40].

b) **Jaundice** and fever developed in a 27-year-old patient following the use of **clorazepate** 15 to 30 mg/day for 2 months. **Bilirubin**, **alkaline phosphatase**, alanine transaminase, and aspartate transaminase were all elevated. Biopsy revealed focal liver cell **necroses**, centrilobular **cholestasis**, and reactive Kupffer cell hyperplasia at 5 months. **Clorazepate** was discontinued 2 months previously [45].

3.3.9] Neurologic Effects

3.3.9.A] Clorazepate Dipotassium

3.3.9.A.1] Akathisia

a) Two cases were reported in which **clorazepate** was implicated in causing **akathisia**. One patient with **psychosis** resulting from **head trauma** had been treated with **thiothixene**; **clonazepam** 6 mg/d was added to her drug regimen and **akathisia** developed within a few days. **Clonazepam** was discontinued; **lorazepam** was begun and 5 months later **clorazepate** 3.75 mg/d was added. When the **clorazepate** dose was increased to 22.5 mg/d, **akathisia** reappeared and subsided when **clorazepate** was discontinued. In the second case, a male patient with seizure disorder resulting from **head trauma** was treated with **carbamazepine** to which **clorazepate** 15 mg/d was added. After 3 weeks severe **akathisia** developed; reduction of the **clorazepate** dose to 1.875 mg every other day led to resolution of the **akathisia** [41].

3.3.9.A.2] Amnesia

a) The results of 3 studies show that **clorazepate** does not impair memory in healthy young or older adults [42] [43] [44]. In a double-blind, placebo-controlled, parallel, single-dose study in 43 healthy geriatric subjects (60 to 74 years), **clorazepate** 3.75 mg and 7.5 mg were found to have no anterograde amnesic effects as evaluated by a modified version of the Williams Word Memory Task (MWW) [42]. Seventy-four healthy young adults (18 to 35 years) were studied in a placebo-controlled, parallel, single-dose study comparing the amnesic effects of **clorazepate** 7.5 mg and 15 mg, **lorazepam** 1 mg and 2 mg, and placebo [43]. The MWW was given before drug administration and at 1, 2, 3, 8, and 24 hours post-dose. Only the 2 mg **lorazepam** group showed significant **memory impairment** at the 1-, 2-, and 3-hour tests. **Clorazepate** at both doses showed no amnesic effect at any time compared with placebo. Ten healthy subjects (21 to 40 years) were studied in a double-blind, placebo-controlled, crossover, single-dose study on the amnesic effects of **clorazepate** 7.5 mg and 15 mg, **diazepam** 5 mg and 10 mg, and **lorazepam** 1 mg and 2 mg. A word list recall test was used to measure drug effect on memory and was given before drug administration and at 30, 60, 90, and 120 minutes post-dose. Neither **clorazepate** nor **diazepam** were associated with amnesic effects when compared with placebo. **Lorazepam** at both doses had significantly greater effect than placebo [44].

3.3.9.A.3] Ataxia

a) Ataxia has been reported in patients who received **clorazepate** dipotassium [40].

3.3.9.A.4] Confusion

a) Mental confusion has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.5] Dizziness

a) Dizziness has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.6] Feeling nervous

a) Nervousness has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.7] Headache

a) Headache has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.8] Insomnia

a) Insomnia has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.9] Slurred speech

a) Slurred speech has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.9.A.10] Somnolence

a) Drowsiness was the most frequently reported side effect reported with [clorazepate](#) dipotassium therapy [40].

3.3.9.A.11] Tremor

a) Tremor has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.10] Ophthalmic Effects

3.3.10.A] [Clorazepate](#) Dipotassium

3.3.10.A.1] Blurred vision

a) Blurred vision has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.10.A.2] [Diplopia](#)

a) [Diplopia](#) has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.12] Psychiatric Effects

3.3.12.A] [Clorazepate](#) Dipotassium

3.3.12.A.1] Depression

a) Depression has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.12.A.2] Irritability

a) Irritability has been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.12.A.3] Personality disorder

- a) A number of reports indicate that [clorazepate](#) may be associated, when used in relatively higher doses, with dramatic personality and behavior changes characterized by rage, depression, irritability, and aggressive behavior [47] [48] [49] [50].
- b) A 7-year-old female accidentally ingested [clorazepate](#) 37.5 mg and developed a rage reaction characterized by the development of hysterical rage. The patient attacked her sister with a knife and ran through the house destroying furniture and dishes. The patient had no history of any such behavior and subsequently became sleepy, but was oriented. The patient was restrained and hospitalized with no further violent outbursts [47].
- c) Of 17 patients with [temporal lobe epilepsy](#) who were treated with [clorazepate](#) 22.5 mg/day or more, 8 patients exhibited personality changes. Four patients demonstrated violent outbursts in addition to symptoms of depression, irritability, and aggressive behavior. It was also noted that 6 of these 8 patients also received [primidone](#) alone or in combination with other anticonvulsants ([phenytoin](#), [phenobarbital](#)). Discontinuation of [clorazepate](#) resulted in resolution of the behavior and personality changes indicating that the effect was reversible. The authors postulated that patients with [temporal lobe epilepsy](#) and receiving [primidone](#) may be susceptible to the side effect and that there may be a possible drug interaction between [primidone](#) and [clorazepate](#) [48].
- d) Other authors questioned the cause and effect relationship between [clorazepate](#) and personality changes citing data suggesting that there is a direct relationship between the suppression of [epileptic seizures](#) by anticonvulsant drug therapy and the appearance of behavioral disturbances in some patients. They indicated that the disturbances varied from case to case but consisted mostly of restlessness, irritability, hyperactivity, frequent temper outbursts, and belligerence. In addition they cited their own data (unpublished) in 65 patients with various types of seizures including psychomotor (temporal lobe) seizures and did not encounter any aberrations of personality or behavior [49].

3.3.12.A.4] Suicidal thoughts

a) Antiepileptic drugs (AEDs) have been associated with an approximate 2-fold increased risk of suicidal thinking or behavior compared with placebo (adjusted relative risk, 1.8; 95% confidence interval, 1.2 to 2.7), based on a pooled analysis of 199 placebo-controlled clinical studies of 11 different AEDs used for several different indications. The analysis included 27,863 AED-treated patients and 16,029 placebo-treated patients between 5 and 100 years of age. There was also an increased risk of suicidal behavior or ideation among the AED-treated patients compared with placebo-treated patients (0.43% vs 0.24%). The increased risk of suicidality was noted as early as 1 week after AED initiation and continued to study completion (24 weeks) in some cases. When compared with placebo, reports of suicidality were generally consistent among all drugs tested and across a range of indications. Close monitoring of patients treated with AEDs for emergence or worsening of depression, suicidal thoughts or behaviors, and other unusual changes in mood or behavior is recommended [40].

3.3.13] Renal Effects

3.3.13.A] [Clorazepate](#) Dipotassium

3.3.13.A.1] Genitourinary symptoms

a) Genitourinary complaints (unspecified) have been reported in patients who received [clorazepate](#) dipotassium [40].

3.3.13.A.2] [Renal function tests](#) abnormal

- a) **Abnormal kidney function** tests have been reported in patients who received **clorazepate** dipotassium [40].

3.3.16| Other

3.3.16.A| **Clorazepate**

3.3.16.A.1| **Drug withdrawal**

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.B| **Clorazepate** Dipotassium

3.3.16.B.1| **Fatigue**

- a) Fatigue has been reported in patients who received **clorazepate** dipotassium [40].

3.3.16.B.2| **Withdrawal sign or symptom**

- a) Physical and psychological dependence may occur with **clorazepate**. Withdrawal effects (eg, nervousness, insomnia, irritability, diarrhea, muscle aches, and **memory impairment**) have developed following the abrupt discontinuation when **clorazepate** has been used for several months. Severity of withdrawal symptoms increase with larger doses and longer treatment durations. Gradual dose reduction is recommended [40].

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) **Teratogenicity** with **clorazepate** has not been confirmed; however, other benzodiazepines such as **diazepam** have demonstrated teratogenic potential [190]. Use of **clorazepate** during pregnancy is not recommended. 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 [191]. In contrast to benzodiazepines, the non-benzodiazepines **zolpidem** and **zaleplon** are in Pregnancy Risk Categories B and C, respectively [192] [193]. The manufacturer maintains a North American Antiepileptic Drug (NAAED) Pregnancy Registry to monitor the effects of in utero exposure to **clorazepate** dipotassium. Patients are encouraged to report pregnancies and to obtain more information by calling 1-888-233-2334. Patients may also

obtain information on the NAAED on the website: www.aedpregnancyregistry.org/. Healthcare providers cannot register patients for the NAAED. Registration must be done by the patient [40].

4) Literature Reports

a) Use of minor tranquilizers such as [diazepam](#), [chlordiazepoxide](#), or [meprobamate](#) during the first trimester of pregnancy may increase risk for [congenital malformations](#). Although it has not been studied thoroughly, [clorazepate](#) dipotassium is a derivative of benzodiazepine, and may be associated with an increased risk for fetal abnormalities [40].

b) [Clorazepate](#) has not been adequately studied to determine an association with an increased risk of fetal anomalies. In a single case of first-trimester maternal overdose with [clorazepate](#), extensive malformations and neonatal death resulted [184]. Neurologic depression in 4 exposed newborns has also been reported [185]. After single dose administration during labor, no clinical repercussions were noted in the neonate; however, the authors cautioned that chronic [clorazepate](#) use in pregnancy cause accumulation of nordiazepam in the fetus [186] [187]. Nordiazepam crosses the placenta more rapidly and is eliminated more slowly than [clorazepate](#).

c) 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 [188].

d) 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. 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 [189].

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)) Nordiazepam, the primary metabolite, is excreted in human breast milk, the manufacturer does not recommend the use of [clorazepate](#) dipotassium in lactating women. The manufacturer maintains a North American Antiepileptic Drug (NAAED) Pregnancy Registry to monitor the effects of in utero exposure to [clorazepate](#) dipotassium. Patients are encouraged to report pregnancies and to obtain more information by calling 1-888-233-2334. Patients may also obtain information on the NAAED on the website <http://www.aedpregnancyregistry.org/>. Healthcare providers cannot register patients for NAAED. Registration must be done by the patient [40]. If exposed, newborns and premature infants should be monitored for sedation or poor feeding, especially if use is prolonged, since the active metabolite could accumulate in the infant's plasma [194].

3)) Literature Reports

a)) Nordiazepam (desmethyldiazepam), a metabolite of [clorazepate](#), has been found in breast milk and in the blood of neonates exposed via breast milk after maternal ingestion of the parent drug during labor [194]. Milk concentrations of up to 15 ng/mL were measured following a single 20 mg [IM injection](#) of [clorazepate](#), representing 15 to 30% of maternal serum levels. No data is available on milk levels with oral [clorazepate](#) therapy [187].

b)) Other benzodiazepines have been associated with symptoms such as lethargy, sedation, and weight loss in the nursing infants exposed to via breast milk [195].

4)) Drug Levels in Breastmilk**a)) [Clorazepate](#) Dipotassium****1)) Parent Drug****a)) Milk to Maternal Plasma Ratio**

1)) 0.18 to 0.24 [204]

2)) Active Metabolites**a)) Nordiazepam [40]**

1)) Milk to Maternal Plasma Ratio

a)] 0.18 to 0.24 [204]

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 [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

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 [96] [97] [98] [99] [100].
- 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 [87] [88] [89] [90] [91].

b)] Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.C] [Amprenavir](#)

- 1) Interaction Effect: an increased risk of [clorazepate](#) toxicity (excessive sedation, confusion, [respiratory depression](#))
- 2) Summary: Plasma concentrations of [clorazepate](#) may be elevated by the concurrent administration of [amprenavir](#). [Amprenavir](#) is an inhibitor of CYP3A4 isoenzyme and may inhibit the metabolism of [clorazepate](#). Although clinical significance is unknown, a decrease in [clorazepate](#) dosing may be warranted [56].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be exercised if [clorazepate](#) 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 [clorazepate](#) 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 [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

3.5.1.E] [Aprobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].
- 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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

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 [85].
- 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 [85].
- 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 [96] [97] [98] [99] [100].
- 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 [87] [88] [89] [90] [91].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

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 [96] [97] [98] [99] [100].
- 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 [87] [88] [89] [90] [91].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

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 [125] [126]. 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 [125] [126]. 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 [170] [171] [172] [173].
- 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](#) [161]. 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 [170] [171] [172] [173].
- 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: [clorazepate](#) 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) [149] [150] [151] [152]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [153] [154]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, nitrazepam, [clonazepam](#)) [155] [156]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [157] [158] [159] [160].
- 3) Severity: minor
- 4) Onset: rapid

- 5) Substantiation: probable
- 6) Clinical Management: Monitor closely for any signs of benzodiazepine toxicity such as sedation, dizziness, or confusion. A benzodiazepine that is eliminated primarily by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) and does not interact with [cimetidine](#) may be an alternative.
- 7) Probable Mechanism: decreased [clorazepate](#) metabolism

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 [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

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 [170] [171] [172] [173].
- 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 [165]. 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](#) [165]. It is suspected that dong quai

may affect other drugs metabolized by the cytochrome P450 enzymes which metabolize [diazepam](#). Caution is advised.

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: theoretical

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

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

8J) Literature Reports

aJ) *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 (Cmax) 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](#) Cmax 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 [164].

bJ) *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 [164].

3.5.1.Q| [Ethchlorvynol](#)

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [174].

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.R| [Evening Primrose](#)

1J) Interaction Effect: reduced anticonvulsant effectiveness

2J) Summary: Evening primrose oil contains gamolenic acid (GLA), which may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [78]. Evening primrose oil is contraindicated in patients with [epilepsy](#) [79] [80].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants. Evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [78].

7J) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.SJ Fentanyl

1J) Interaction Effect: increased risk of CNS depression

2J) 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 [148]. 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](#) [84]. 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 [148].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [148].

7J) Probable Mechanism: additive CNS depression

3.5.1.TJ Flumazenil

1J) Interaction Effect: precipitation of seizures

2J) 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 [71].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [71].

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

3.5.1.UJ Fosamprenavir

1J) Interaction Effect: an increased risk of [clorazepate](#) toxicity (excessive sedation, confusion, [respiratory depression](#))

2J) Summary: Plasma concentrations of [clorazepate](#) may be elevated by the concurrent administration of [fosamprenavir](#). [Amprenavir](#), the active metabolite of [fosamprenavir](#), is an inhibitor of CYP3A4 isoenzyme and may inhibit the metabolism of [clorazepate](#). Although clinical significance is unknown, a decrease in [clorazepate](#) dosing may be warranted [133].

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Caution should be exercised if [clorazepate](#) and [fosamprenavir](#) are administered concurrently. Monitor the patient for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#). A decrease in [clorazepate](#) dose may be necessary [133].

7J) Probable Mechanism: inhibition of CYP3A4-mediated [clorazepate](#) metabolism by [amprenavir](#), the active metabolite of [fosamprenavir](#)

3.5.1.V] Fospropofol

1J) Interaction Effect: additive cardiorespiratory effects

2J) Summary: Concomitant use of fospropofol and a benzodiazepine may result in additive cardiorespiratory effects due to the sedative action of both drugs [52]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and a benzodiazepine are used in combination. A reduction in dose of one or both drugs may be necessary.

7J) Probable Mechanism: CNS depression

3.5.1.W] Ginkgo

1J) Interaction Effect: decreased anticonvulsant effectiveness

2J) Summary: In a case report, 2 patients with [epilepsy](#) previously well controlled by [valproate](#) sodium developed a recurrence of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn [130]. An infant developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds [131]. The compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as in leaves, the ginkgo component from which commercially available extracts are derived [132]. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridoxine is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known seizure disorders).

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with [epilepsy](#). If seizures occur for the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxine is present.

7J) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may cause seizures

8J) Literature Reports

aJ) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine levels. The serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for the tonic/[clonic convulsions](#) and loss of consciousness observed. They further observed that infants are particularly vulnerable [127].

bJ) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of Ginkgo biloba leaves which is the source of commercially-available products.

Highest amounts were found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was detected in medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested [128].

c) Seizures recurred in 2 patients, both with [epilepsy](#) that was well controlled prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without changing [anticonvulsant therapy](#)) after discontinuing Gb [129].

3.5.1.X] [Hydrocodone](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) 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 [176].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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 [176].
- 7) Probable Mechanism: additive CNS depression

3.5.1.Y] [Hydromorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].

- 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 [81].

3.5.1.Z] 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](#) [113]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [114].
- 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 [112].

3.5.1.AA] [Levorphanol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

3.5.1.AB] [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 [162] and use with caution [163].

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 [162] and use with caution [163].

7)) Probable Mechanism: additive CNS depression

3.5.1.AC] [Magnolia](#)

1)) Interaction Effect: increased central nervous system depression

2)) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [120] [121] [122]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [123]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [124]. 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 [115].

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 [116].

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 [117].

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) [118].

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 [119].

3.5.1.AD) [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](#) [143] [144] [145] 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](#) [143] [144] [145] 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.AE] Meperidine

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

2J) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].

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 [81].

3.5.1.AF] Mephenesin

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [170] [171] [172] [173].

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.AG] Mephobarbital

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.AH] [Meprobamate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [170] [171] [172] [173].
- 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] [Metaxalone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [170] [171] [172] [173].
- 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.AJ] [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 [77].
- 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 [77].

7) Probable Mechanism: additive CNS depression effects

3.5.1.AK] [Methocarbamol](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [170] [171] [172] [173].

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.AL] [Methohexital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.AM] [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 [86].

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 [86].
- 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 [86].

3.5.1.AN] [Morphine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

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

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

3.5.1.AP| Omeprazole

- 1) Interaction Effect: an increased risk of [clorazepate](#) toxicity
- 2) Summary: Cytochrome isoenzymes CYP2C19 and CYP3A4 are responsible for the metabolism of [omeprazole](#) and [clorazepate](#). [Omeprazole](#) has an inhibitory effect on the metabolism of [clorazepate](#) and its metabolite desmethyldiazepam that may prove clinically relevant. Short-term administration of [omeprazole](#) with dipotassium [clorazepate](#) can lead to a serious accumulation of [clorazepate](#) levels. Drugs of choice for [stress ulcer](#) prophylaxis for intensive care patients are those that are not metabolized by cytochrome P450 enzymes. Ranitidine, [sucralfate](#), and [pantoprazole](#) are not expected to show any clinically significant interaction with drugs that affect the hepatic cytochrome P450 system [55].
- 3) Severity: major
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: [Omeprazole](#) has an inhibitory effect on the metabolism of [clorazepate](#) and its metabolite desmethyldiazepam that may prove clinically relevant. Short-term administration of [omeprazole](#) with dipotassium [clorazepate](#) can lead to a serious accumulation of [clorazepate](#) levels. Intensive care patients should be administered drugs for [stress ulcer](#) prophylaxis that do not significantly affect the hepatic cytochrome P450 system, such as [ranitidine](#), [sucralfate](#), or [pantoprazole](#). None of these drugs are expected to show any clinically significant interaction with commonly prescribed medications in the intensive care unit. Potentially dangerous and unforeseeable adverse events may occur if this point is not observed.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) A 60-year-old male with a history of [essential hypertension](#), [alcohol-induced fatty liver](#) without [hepatic cirrhosis](#), and chronic smoker's [cough](#) was admitted to a hospital for [alcohol detoxification](#) therapy. Treatment with intravenous dipotassium [clorazepate](#) was initiated on hospital day 5. The patient became unconscious within 29 hours and dipotassium [clorazepate](#) therapy was discontinued. The patient was administered a total of 1500 mg of dipotassium [clorazepate](#), intravenous [omeprazole](#) 80 mg/day for [stress ulcer](#) prophylaxis, [furosemide](#), thiamine, [heparin](#), glucose, and electrolyte solutions. For several days the patient remained somnolent and comatose. Serum concentrations of the major active metabolite of dipotassium [clorazepate](#), desmethyldiazepam, was 2100 mcg/L (therapeutic range 200-1000 mcg/L) seven days after dipotassium [clorazepate](#) was discontinued. The half-life of desmethyldiazepam can range from 30 to 200 hours. The half-life in this case is estimated to be approximately 550 hours. The patient showed signs of improvement thirteen days after dipotassium [clorazepate](#) therapy was discontinued. [Clorazepate](#), like [omeprazole](#), is metabolized via the cytochrome P450 2C19 and 3A4 isoenzymes. When these two drugs are administered concomitantly a serious accumulation of [clorazepate](#) levels can occur. In this case, the extended half-life of desmethyldiazepam is most likely due to an interaction between [omeprazole](#) and dipotassium [clorazepate](#). The high dose of dipotassium [clorazepate](#), however, in conjunction with reduced metabolic capacity from alcohol-induced liver damage may have contributed as well [54].

3.5.1.AQ| Orlistat

- 1) Interaction Effect: reduced anticonvulsant effectiveness
- 2) Summary: Concomitant use of [orlistat](#) with [anticonvulsant therapy](#) has resulted in reports of convulsions during postmarketing surveillance of [orlistat](#). Therefore, if coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [51].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [orlistat](#) with an anticonvulsant may result in reduced efficacy of the anticonvulsant. If coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [51].
- 7) Probable Mechanism: unknown

3.5.1.AR] [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 [139] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [140].
- 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 [139] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [140].
- 7) Probable Mechanism: additive effects

3.5.1.AS] [Oxymorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].
- 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 [81].

3.5.1.AT] [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 [103]. 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 [103]. 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 [103].

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 [134]. 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 [135]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [136].

3.5.1.AU] [Pentobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.AV] [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 [175].
- 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 [175].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AW] [Phenobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].
- 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 [87] [88] [89] [90] [91].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.AX] [Primidone](#)

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

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.AY] [Propoxyphene](#)

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].

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 [81].

3.5.1.AZ| [Remifentanyl](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].

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 [81].

3.5.1.BA| [Ritonavir](#)

1) Interaction Effect: an increased risk of extreme sedation and confusion

2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [clorazepate](#), causing a potential risk of extreme sedation and [respiratory depression](#) [137]. A decrease in benzodiazepine dose may be needed [138].

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 [clorazepate](#) as required.

7) Probable Mechanism: increased [clorazepate](#) serum concentrations due to decreased [clorazepate](#) metabolism

3.5.1.BB| [Saquinavir](#)

1) Interaction Effect: increased [clorazepate](#) plasma concentrations

2) Summary: Coadministration of [saquinavir](#) (strong CYP3A4 inhibitor) and a benzodiazepine, such as [clorazepate](#), may result in increased benzodiazepine plasma concentrations. If the concomitant use of [clorazepate](#) with [saquinavir](#) is necessary, consider dose reductions of [clorazepate](#) when necessary [147].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [clorazepate](#) with [saquinavir](#) may lead to increased [clorazepate](#) plasma concentrations. If coadministration is required, a dose reduction of [clorazepate](#) may be warranted [147].

7) Probable Mechanism: unknown

3.5.1.BC] [Secobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [92]. 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 [93]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.BD] [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 [168] [169]. 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 [166].

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](#) [167].

3.5.1.BE] [Sodium Oxybate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [53]. 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.BF] [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 [72] [73] [74] [75]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [72]. 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 [72] [73] [74] [75]. 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.

7j) Probable Mechanism: induction of CYP3A4-mediated metabolism of the benzodiazepine by St. John's wort

8j) 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 C_{max} 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 T_{max} and t(1/2) and 2-oxoquazepam C_{max}, AUC, T_{max}, and t(1/2) were not significantly affected by St. John's wort. The 2-oxoquazepam to quazepam ratio in the C_{max} 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 [72].

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) [73].

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 [76].

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 C_{max} 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 [74].

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) [75].

3.5.1.BG| [Sufentanil](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [82]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [83]. 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](#) [84].

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 [81].

3.5.1.BH| [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 [101].

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 [101].

7J) Probable Mechanism: additive CNS depression

3.5.1.BI] Tan-Shen

1J) Interaction Effect: increased risk of central nervous system depression

2J) Summary: Miltirone and the other nine diterpene quinones present in *Salvia miltiorrhiza* (Tan-shen) appear to act as partial agonists at central benzodiazepine receptors [142]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [142]. 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.

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: theoretical

6J) 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.

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

8J) Literature Reports

aJ) 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) [141]. 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](#) [141].

3.5.1.BJ] Tapentadol

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

2J) 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 [146].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [146].

7J) Probable Mechanism: additive effects

3.5.1.BK] Teduglutide

1J) Interaction Effect: increased exposure of orally administered benzodiazepines

2J) 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 [102]. 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 [102]. Monitor for increased benzodiazepine side effects if a patient is taking teduglutide concomitantly with an oral benzodiazepine.

7) Probable Mechanism: unknown

8) Literature Reports

a) 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 [102].

3.5.1.BL| [Theophylline](#)

1) Interaction Effect: decreased benzodiazepine effectiveness

2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [66] [67] [68] [69]. 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 [70].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) 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.

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

8) Literature Reports

a) 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 [57].

b) 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 [58]. Other studies and case reports have also shown that theophylline antagonizes the sedative effects of diazepam [59] [60].

c) Three case reports described patients who had the sedative effects of lorazepam reversed postoperatively by the administration of aminophylline 1 mg/kg intravenously [61]. This same aminophylline dose was used to reverse the sedative effects of midazolam in three other patients [62]. Theophylline also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [63].

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 [64].

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 [65].

3.5.1.BM] Thiopental

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [96] [97] [98] [99] [100].

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 [87] [88] [89] [90] [91].

b) Concomitant administration of intravenous midazolam and thiopental resulted in synergistic (supraadditive) effects during induction of anesthesia [92]. 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 [93]. A 15% reduction in the thiopental induction dose requirement has been observed if it

follows intramuscular premedication with [midazolam](#) [94]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [95].

3.5.1.BN| 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 [103]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [111] [104]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [104]. 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 [103]. 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 [103] [104]. 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 [103].

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 [105]

[106]. *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 [107]. 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 [108]. 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 [109].

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* [110].

3.5.1.BO| 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 [177].
- 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 [177].
- 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 clorazepate
- 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 [180] [181] [182].
- 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 [179].

3.5.2.B) Ethanol

1) Interaction Effect: increased sedation

2) Summary: Concomitant ethanol and [clorazepate](#) therapy may result in excess central nervous system and [respiratory depression](#). A slightly increased optic reaction time with decreased endurance and concentration following concomitant [clorazepate](#) 20 mg and ethanol 1 g/kg has been reported [178].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients receiving [clorazepate](#) should be advised against ethanol use.

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) [Clorazepate](#) Dipotassium

1) Therapeutic

a) Improvement in the clinical signs and symptoms of condition being treated, ie, tension, nervousness, anxiety.

2) Toxic

a) Excessive CNS depression, ie, drowsiness, lethargy, etc.

b)) Personality changes, ie, hostility, aggressiveness.

4.2] Patient Instructions

A)) Clorazepate (By mouth)

Clorazepate

Treats anxiety, trouble sleeping, symptoms of alcohol withdrawal, and certain types of [epilepsy](#) (seizures). Belongs to a class 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 [clorazepate](#) or to other benzodiazepine medicine (such as [Halcion®](#), [Librium®](#), or [Valium®](#)). You should not use this medicine if you have a [narrow angle glaucoma](#).

How to Use This Medicine:

Capsule, Tablet, Long Acting Tablet

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.

Swallow the extended-release tablet whole. Do not crush, break, or chew it.

You may take this medicine with or without food.

This medicine may be used with other seizure medicines. Keep using all of your seizure medicines unless your doctor tells you to stop.

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:

Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

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.

Make sure your doctor knows if you are also using hexobarbital (Evipan®), [phenobarbital](#) (Luminal®), a phenothiazine medicine (such as [prochlorperazine](#), [Compazine®](#), [Mellaril®](#), [Phenergan®](#), [Thorazine®](#), or [Trilafon®](#)), or an MAO inhibitor (MAOI) such as [Eldepryl®](#), [Marplan®](#), [Nardil®](#), or [Parnate®](#).

Do not drink alcohol while you are using this medicine.

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

Warnings While Using This Medicine:

Make sure your doctor knows if you have [kidney disease](#), liver disease, [glaucoma](#), lung disease, or a history of mental illness or depression.

It is important to tell your doctor if you become pregnant while using this medicine. Your doctor may want you to join a pregnancy registry for patients taking a seizure medicine.

You should not breastfeed if you are using this medicine.

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.

Do not stop using this medicine suddenly. Your doctor will need to slowly decrease your dose before you stop it completely.

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.

For some children, teenagers, and young adults, this medicine can increase thoughts of suicide. Tell your doctor or your child's doctor right away if you or your child start to feel more depressed and have thoughts about hurting yourselves. Report any unusual thoughts or behaviors that trouble you or your child, especially if they are new or get worse quickly. Make sure the doctor knows if you or your child have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell the doctor if you or your child have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let the doctor know if you, your child, or anyone in your family has **bipolar disorder** (manic-depressive) or has tried to commit suicide.

Older adults and children may be more sensitive to side effects than other patients.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Blood tests may be needed to check for unwanted effects.

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

Difficulty with breathing.

Feeling agitated, confused, sad, or irritable.

Fever, chills, **cough**, sore throat, and body aches.

Hallucinations (seeing, hearing, or feeling things that are not there).

Problems with balance or walking.

Severe muscle weakness or difficulty with standing.

Slurred speech or severe drowsiness.

Tremors.

Unusual behavior or thoughts of hurting yourself.

Unusual tiredness or weakness.

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

Blurred or double vision.

Constipation, diarrhea, or upset stomach.

Difficulty with concentrating or memory loss.

Drowsiness, dizziness, or clumsiness.

Dry mouth.

"Hangover" effects after bedtime use.

Headache.

Skin rash.

Trouble with sleeping.

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

4.3] Place In Therapy

A) **Clorazepate** Dipotassium

1) Acute Alcohol Withdrawal

a)) **Clorazepate** is indicated for the symptomatic relief of acute alcohol withdrawal [1] [2]. It was shown to be effective in reducing symptoms associated with alcohol withdrawal according to an uncontrolled study (n=226) [22] and a double-blind, placebo-controlled study [23].

2)) Anxiety

a)) **Clorazepate** is indicated for the management of anxiety disorders or for the short-term relief of symptomatic anxiety. Anxiety or tension related to the stresses of everyday life usually do not require anxiolytic therapy. The efficacy of long term use for more than 4 months for the treatment of anxiety has not been assessed by clinical studies [1] [2].

3)) Partial Seizures

a)) **Clorazepate** is indicated as adjunctive therapy in the management of partial seizures. Long term studies in epileptic patients have demonstrated continued therapeutic activity [1] [2].

4.4] Mechanism of Action / Pharmacology

A)) **Clorazepate** Dipotassium

1)) Mechanism of Action

a)) **Clorazepate** dipotassium is a benzodiazepine anxiolytic with depressant effects on the central nervous system. **Clorazepate** dipotassium is rapidly metabolized to the primary metabolite nordiazepam [40].

4.5] Therapeutic Uses

4.5.A] **Clorazepate** Dipotassium

4.5.A.1] **Alcohol withdrawal syndrome**

FDA Labeled Indication

a)) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b)) Summary:

Indicated for the symptomatic relief of acute alcohol withdrawal [1] [2]

Clorazepate is effective in reducing symptoms associated with alcohol withdrawal according to an uncontrolled study (n=226) [22] and a double-blind, placebo-controlled study [23].

c)) Adult:

1)) **CLORAZEPATE** was reported effective in reducing alcohol withdrawal symptoms and seizures following abrupt alcohol discontinuation in an uncontrolled study involving 226 patients [22]. All patients were administered **CLORAZEPATE** 15 milligrams orally four times a day on the first day, followed by 15 milligrams three times a day on the second day and 15 milligrams twice a day on day three; on days four and five, doses of 15 and 7.5 milligrams were given at bedtime, respectively. Supplemental doses of 15 milligrams were administered when required. In addition, all patients were given **MAGNESIUM SULFATE** 2 grams intramuscularly upon admission, followed by 1 gram intramuscularly every four hours for 3 doses. No convulsions were observed in any patient, and withdrawal symptoms were reduced.

2)) A series of patients were treated with 7.5 to 15 milligrams three to four times a day orally for 4 weeks in the treatment of anxiety secondary to alcohol withdrawal [23]. The study was double-blind, placebo-controlled and **CLORAZEPATE** was compared with **DIAZEPAM**. Results indicated that there was significant improvement in the patient's anxiety with both **CLORAZEPATE** and **DIAZEPAM** as compared with placebo, but there were no significant differences between the 2 drugs.

4.5.A.2] Anxiety

FDA Labeled Indication

a)) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: **RECOMMENDATION AND EVIDENCE RATINGS**

b)) Summary:

Indicated for the management of anxiety disorders or for the short-term relief of symptomatic anxiety [1] [2].

Anxiety or tension related to the stresses of everyday life usually do not require anxiolytic therapy [1] [2].

Efficacy of long term use for more than 4 months for the treatment of anxiety has not been assessed by clinical studies [1] [2]

A number of studies have indicated that **clorazepate** is superior in the treatment of anxiety and other accompanying **psychoneurosis** to placebo. Results of these studies indicate that response is considered good to excellent in the majority of patients as measured by overall Global response, Hamilton anxiety rating scores, and Kellner-Sheffield symptom rating scores [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15].

c)) Adult:

1)) **Clorazepate** significantly improved measurements of anxiety and high levels of depressed mood compared with placebo in a double-blind, placebo-controlled study [16]. The 189 patients with **generalized anxiety disorder** were divided into a low depressed-mood severity group (n=80) or high depressed-mood severity group (n=109) based on scores on the **Zung Self-Rating Depression Scale** (SDS). **Clorazepate** 15 milligrams (mean daily dose) was given to 103 subjects during week 1,

and 19.5 mg (mean daily dose) was given during weeks 2 and 3; placebo was given to 86 subjects. The high depressed-mood group treated with [clorazepate](#) improved significantly in anxiety and depressed mood at 7 and 21 days compared with placebo as measured by the Hamilton Rating Scale for Anxiety (HAM), the Zung Self-Rating Anxiety Scale (SAS), and the SDS. The low depressed-mood group showed significant improvement in anxiety as measured by HAM, but no significant differences were measured by the SAS or SDS.

2)) A number of studies indicate that [clorazepate](#) in doses ranging from 10 to 100 milligrams/day in divided doses administered orally or parenterally is effective in reducing the anxiety in patients undergoing various minor or major surgeries [17] [18] [19].

4.5.A.3] Epilepsy

a)) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

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

Recommendation: Adult, Class IIb; [Pediatric, Class IIb](#)

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

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

b)) Summary:

[CLORAZEPATE](#) has been utilized in the treatment of seizure disorders with varying rates of success [24] [25] [26] [27] [28].

c)) Adult:

1)) A 23% response to [CLORAZEPATE](#) was reported in patients with refractory SEIZURES not controlled with [PHENOBARBITAL](#), [PRIMIDONE](#), [PHENYTOIN](#), [CARBAMAZEPINE](#), [VALPROIC ACID](#) or combinations of these drugs [28] Although clinical improvement was seen, there was no improvement in EEG. The dose of [CLORAZEPATE](#) ranged from 45 to 288 milligrams daily. These results are similar to those of Feldman, who reported a decrease in [psychomotor seizures](#) [27]. In another study, [CLORAZEPATE](#) was reported to be of no benefit in the treatment of [psychomotor seizures](#) [25].

2)) A series of 59 patients (aged 7 months to 45 years) were treated with [CLORAZEPATE](#) 0.4 to 2 milligrams/kilogram/day in 1 to 4 divided doses over 0.5 to 2 years for various kinds of [epileptic disorders](#) [26]. The results indicated [CLORAZEPATE](#) alone did not maintain complete seizure control for any patient, but when used in combination with other standard antiepileptic drugs, the doses of those drugs were reduced. [CLORAZEPATE](#) may be useful as adjunctive therapy in intractable minor seizures.

d)) Pediatric:

1)) [Clorazepate](#) was effective in controlling severe generalized seizures in 11 children (range 3 to 17 years) whose seizures had been inadequately controlled by conventional anticonvulsants [29]. Seven of the children were treated with [valproate](#) plus [clorazepate](#) 3.75 mg given 2 to 4 times daily. Four children were treated with [clorazepate](#) alone. Seizure control was maintained with [clorazepate](#) serum levels at or near the lower limit of the therapeutic range (0.5 to 1.5 mcg/mL). After a year, recurrent seizures caused 3 subjects to discontinue [clorazepate](#), but one was restarted after 6 months with good results.

2j) A series of 59 patients (aged 7 months to 45 years) were treated with [CLORAZEPATE](#) 0.4 to 2 milligrams/kilogram/day in 1 to 4 divided doses over 0.5 to 2 years for various kinds of [epileptic disorders](#) [26]. The results indicated [CLORAZEPATE](#) alone did not maintain complete seizure control for any patient, but when used in combination with other standard antiepileptic drugs, the doses of those drugs were reduced. [CLORAZEPATE](#) may be useful as adjunctive therapy in intractable minor seizures.

4.5.A.4] Partial seizure; Adjunct

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(9 years or older\)](#)

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

Recommendation: Adult, Class IIb; Pediatric, Class IIb

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

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

b) Summary:

Indicated as adjunctive therapy in the management of partial seizures [1] [2]

Long term studies in epileptic patients have demonstrated continued therapeutic activity [1] [2].

4.5.A.5] Spasticity

a) Overview

FDA Approval: Adult, no; [Pediatric, no](#)

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

b) Summary:

Decreased spasticity but not rigidity in a small double blind study [30]

c) Adult:

1j) [Clorazepate](#) lessened spasticity but not rigidity in a double blind, placebo-controlled, crossover study [30]. Eight patients were studied; 4 patients with [multiple sclerosis](#) had spasticity and 4 with [encephalopathy](#) had both spasticity and rigidity. Subjects were given [clorazepate](#) 5 milligrams every 12 hours for 10 days with a 7-day washout period before crossover. Clinical signs of spasticity and ankle reflex measurements significantly improved in all 8 patients during the chlorazepate treatment period. No improvement was seen with placebo.

4.5.A.6] Tardive dyskinesia

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

b) Summary:

Some improvement in [tardive dyskinesia](#) seen in a small case series [31]

c) Adult:

1) Twelve patients (age range 61 to 86 years) with [tardive dyskinesia](#) were treated with 15 to 45 milligrams/day (mean dose=27 milligrams) for 6 weeks with [CLORAZEPATE](#) [31]. Results indicated that most patients demonstrated slight to marked improvement in [tardive dyskinesia](#) and psychiatric symptoms.

4.5.A.7] Tetanus

a) Overview

FDA Approval: Adult, no; **Pediatric, no**

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

b) Summary:

A case series demonstrated some effect in patients with stage I to III [tetanus](#) [32]

c) Adult:

1) A series of 35 patients with stage I-III [tetanus](#) were treated with 100 to 1600 milligrams/day doses of [CLORAZEPATE](#) (parenterally or orally) for sedation of paroxysms [32]. Results indicate that in patients with stage I [tetanus](#), administration of [CLORAZEPATE](#) by the oral route resulted in rapid and satisfactory sedation in all cases. In patients with stage II [tetanus](#), intravenous infusion of [CLORAZEPATE](#) proved to be most effective in doses greater than or equal to 500 milligrams/day. In patients with stage III [tetanus](#) the drug proved to be satisfactory in doses greater than 1 gram/day in 4 to 7 patients. Three patients in stage III [tetanus](#) were noted to develop as intense polypnea with a frequency of 80 minute which interfered with [artificial respiration](#).

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Alpidem

4.6.A.1] Anxiety

a) Alpidem is of comparable efficacy to [clorazepate](#) in the treatment of anxiety. Alpidem 50 mg 3 times a day was compared with [clorazepate](#) 10 mg 3 times a day for 21 days. Objective testing showed a more

than 50% reduction in symptoms of anxiety with both drugs; according to the Clinical Global Impression (CGI) scale at the end of the study, 67% of patients treated with alpidem and 72% of patients treated with [clorazepate](#), [diazepam](#), or [lorazepam](#) (all 3 groups together) responded to treatment (although the difference was not statistically significant). While the incidence of sedation (somnolence or drowsiness) experienced with alpidem was similar to that seen with the benzodiazepines, the incidence of fatigue and depression was much lower than that which occurred with the benzodiazepines [218].

4.6.B| Bentazepam

4.6.B.1| Anxiety

a) Bentazepam decreased anxiety and did not impair cognitive function when compared to [clorazepate](#) in a 6-week, parallel, randomized, open-label study of 50 patients with anxiety disorders. Twenty-five patients received bentazepam 25 milligrams (mg) 3 times daily, and 25 patients received [clorazepate](#) 10 mg 3 times daily. Hamilton Anxiety Scale scores were lower in both groups throughout the study, but were significantly lower in the bentazepam group at the first, third and sixth weeks compared to the [clorazepate](#) group (p less than 0.001). Statistical improvement in cognitive testing was noted for both groups (p less than 0.01 to 0.05) throughout the study, without significant intergroup differences. At study end, 20 of 21 bentazepam patients showed improvement versus 15 of 19 patients on [clorazepate](#), according to physician assessment (p less than 0.05). One patient in the bentazepam group discontinued treatment due to adverse effects ([tachycardia](#), hypotension, and gastric discomfort), versus 3 patients in the [clorazepate](#) group [212].

4.6.C| Bromazepam

4.6.C.1| Anxiety about treatment, Preoperative

a) In three evaluations given on the evening before (T1), the morning of (T2), and just before surgery (T3) to elderly patients scheduled for ophthalmic surgery and receiving bromazepam, [clorazepate](#), or placebo before each evaluation, the [State-Trait Anxiety Inventory](#) documented a significant anxiolytic effect in patients receiving bromazepam at T1 that was enhanced at T2, while in the groups receiving [clorazepate](#) or placebo no significant differences in anxiety occurred [213]. Twenty patients in each group received bromazepam 3 milligrams, [clorazepate](#)-dipotassium 20 milligrams, or placebo at T1, T2, and T3. The lack of anxiolytic effect in the [clorazepate](#) group was unexpected, as concentrations of the pharmacologically active metabolite of [clorazepate](#) are higher and elimination prolonged in the elderly. However, the quality of sleep during the night before surgery was improved in both treatment groups. Neither treatment group gave indications of over-sedation or hypoxemia while undergoing surgery. In contrast to patients in the other two groups, patients receiving bromazepam evidenced significant impairment of short-term memory at T3, although this impairment did not impact intra-operative cooperation. Comparisons at various doses of the studied drugs would extend these findings.

4.6.D| [Buspirone](#)

1) Adverse Effects

a) Abrupt withdrawal of [chlorazepate](#) (CZ), but not [busPIRone](#) (BP), after long-term treatment of anxious outpatients was shown to result in withdrawal reaction in a double blind, randomized study in 150 patients [216]. Therapy consisted of CZ 15 to 60 mg/d (n=76) or BP 10 to 40 mg/d (n=74) for 24 weeks after which the tranquilizers were suddenly replaced with placebo for 4 weeks (the withdrawal phase). BP-treated patients dropped out of the study at a significantly higher rate than CZ-treated patients (71% vs 43%), leaving 40 CZ-treated patients and 21 BP-treated patients for evaluation. Anxiety assessment scores were similar for both groups by week 4 of the study, but the high dropout rate for BP indicates less patient satisfaction with this agent. During the withdrawal phase, 11

withdrawal symptoms were identified as being significantly more common in the CZ group than the BP group. Significantly more subjects in the CZ group (16 of 40, 40%) took reserve medication during the withdrawal period than in the BP group (0 of 21). Using a criterion of 5 or more new symptoms to define withdrawal, significantly more CZ-treated subjects (27 of 40, 72%) experienced withdrawal than BP-treated subjects (2 of 21, 9%). Because the BP-treated group was so small by the withdrawal phase, Rickels et al recommended further study of the addictive and withdrawal effects of BP with a large patient population.

4.6.E] Clobazam

4.6.E.1] Anxiety

a) One small study reported the comparable efficacy of [clorazepate](#) 15 milligrams daily and clobazam 20 to 30 milligrams daily in the treatment of anxiety in outpatients [217]. [Clorazepate](#) was associated with a higher incidence of drowsiness than clobazam.

4.6.F] [Diazepam](#)

4.6.F.1] Anxiety

a) Numerous studies have indicated that [clorazepate](#) and [diazepam](#) are both effective in treating anxiety and that there are no statistically significant differences between the two agents. Isolated studies indicate that [clorazepate](#) is in certain instances more effective than [diazepam](#) but the results from most of these studies have not yet been confirmed [219]. In a study of 30 patients, [clorazepate](#) in a dose of 7.5 milligrams three times/day was less effective than [diazepam](#) according to Global, Hamilton, Wittenborn, and Zung rating scale assessments [220]. In a series of 90 patients, 32 of whom were treated with [clorazepate](#) in a dosage range of 22.5 to 37.5 milligrams/day, [clorazepate](#) response in patients with chronic anxiety or anxiety [depressive neurosis](#) was substantially better than a response to [diazepam](#) [221]. However, a vast majority of available studies indicated that both [clorazepate](#) and [diazepam](#) are significantly superior to placebo but that these studies (usually double-blind, cross-over, placebo control) have failed to demonstrate any statistically significant difference between the 2 drugs using standard measures of anxiety and tension [222] [223] [224]; (Itil, 1972) [225] [226] [227] [228] [229].

b) Potassium [clorazepate](#) 15 milligrams at bedtime as a single dose was reported to be more effective than oral [diazepam](#) 5 milligrams three times/day in the treatment of anxiety or anxiety/hysteria in one controlled study (Henderson, 1982).

c) [Clorazepate](#) was less effective than either [prazepam](#) (Verstran(R)) or [diazepam](#) in treating anxiety in 60 patients (age 21 to 61 years) as assessed by the Hopkin's Symptoms check-list. However, all 3 drugs were superior to placebo. In this double-blind study, average doses given were [prazepam](#) 40 milligrams/day, [diazepam](#) 22 milligrams/day and [clorazepate](#) 29 milligrams/day for 28 days. The Hamilton Anxiety Scale showed improvement with all 3 drugs but no difference between them [229].

4.6.G] [Halazepam](#)

4.6.G.1] Anxiety

a) [Halazepam](#) 120 mg PO as was reported as effective as [clorazepate](#) 22.5 mg HS in the treatment of outpatients with anxiety in a controlled study [230].

b) [Halazepam](#) 80 to 160 mg HS was compared with [clorazepate](#) 15 to 30 mg HS and placebo in 60 patients with symptoms of anxiety, and tension in a double-blind manner at 6 different centers. Physician rating (global assessments, relative improvement and Hamilton Anxiety Scales) favored both drugs over placebo to a significant extent at the end of weeks 1 to 4. Physician rated measures favored [halazepam](#) over

clorazepate at weeks 3 and 4. Patient rated measures agreed with physician evaluations, however, they did not discriminate as well between drug and placebo groups [231].

4.6.H] Hydroxyzine

4.6.H.1] Alcohol withdrawal syndrome

a) **HydrOXYzine**, as the pamoate salt, is not as effective as the benzodiazepines, including clorazepate (15 mg every 4 hours for agitation followed by 45 mg/first night and 22.5 mg/second night) in the treatment of alcohol withdrawal [208].

4.6.I] Lorazepam

1) Efficacy

a) The results of 2 studies show that lorazepam has greater amnestic effect than clorazepate, diazepam, or placebo in young, healthy adults [206] [207]. Seventy-four healthy young adults (18 to 35 years) were studied in a placebo-controlled, parallel, single-dose study comparing the amnestic effects of clorazepate 7.5 mg and 15 mg, lorazepam 1 mg and 2 mg, and placebo [206]. A modified version of the Williams Word Memory Task was given before drug administration and at 1, 2, 3, 8, and 24 hours post-dose. Only the 2 mg lorazepam group showed significant memory impairment at the 1, 2, and 3-hour tests. Clorazepate at both doses showed no amnestic effect at any time compared with placebo. Ten healthy subjects (21 to 40 years) were studied in a double-blind, placebo-controlled, crossover, single-dose study on the amnestic effects of clorazepate 7.5 mg and 15 mg, diazepam 5 mg and 10 mg, and lorazepam 1 mg and 2 mg [207]. A word list recall test was used to measure drug effect on memory and was given before drug administration and at 30, 60, 90, and 120 minutes post-dose. Neither clorazepate nor diazepam were associated with amnestic effects when compared with placebo. Lorazepam at both doses had significantly greater effect than placebo. Healey et al suggest that the clinical benefits of anterograde amnesia in preoperative sedation make lorazepam the better choice in that setting, whereas clorazepate would be more suitable for the outpatient being treated for anxiety.

4.6.J] Phenobarbital

4.6.J.1] Epilepsy

a) SUMMARY: Clorazepate is similarly effective as phenobarbital for seizure disorders in patients concurrently receiving phenytoin, but may be preferred by patients due to lower CNS effects.

b) Clorazepate was as effective as phenobarbital for control of seizures in 8 outpatients concomitantly stabilized on phenytoin. Doses of 0.56 g/kg/day produced desmethyldiazepam serum levels of 1 to 2 mcg/L which were associated with seizure control. Clorazepate produced no side effects and was preferred over phenobarbital by the patients [209].

c) A randomized, double-blind, crossover study compared clorazepate and phenobarbital in 42 adults with simple or complex partial seizures with or without secondary generalization [210]. All patients received phenytoin throughout the trial in dosages which produced serum concentrations near 20 mg/L. Seizure frequency over 3-month evaluation periods was slightly but not significantly less with clorazepate (average 11.6 per month) than with phenobarbital (18.6 per month). The number of patients experiencing fewer seizures on either clorazepate or phenobarbital was essentially the same. Subjective and objective evidence of toxicity (primarily drowsiness, dizziness, and mental status changes) were significantly more frequent with phenobarbital than with clorazepate (subjectively 75% versus 40%, respectively) and significantly more patients preferred to continue clorazepate (52%) than phenobarbital (12%).

d) One study reported that a combination of clorazepate and phenytoin was similarly effective as a combination of phenobarbital plus phenytoin in patients with partial seizures, with "patient preference"

being in favor of the clorazepate-phenytoin regimen [210]. Toxicity was greater in the phenobarbital-phenytoin regimen. [Clorazepate](#) may be a useful alternative to [phenobarbital](#) when used in combination [phenytoin](#) therapy of partial seizures in patients who develop intolerance to [phenobarbital](#).

4.6.K] [Prazepam](#)

4.6.K.1] Anxiety

a) [Clorazepate](#) was less effective than either [prazepam](#) or [diazepam](#) in treating anxiety in 60 patients (age 21 to 61 years) as assessed by the Hopkin's Symptoms check-list. However, all 3 drugs were superior to placebo. In this double-blind study average doses given were [prazepam](#) 40 mg/day, [diazepam](#) 22 mg/day and [clorazepate](#) 29 mg/day for 28 days [211].

4.6.L] [Trazodone](#)

4.6.L.1] Adjustment disorder - [Cancer](#)

a) SUMMARY: [TRAZODONE](#) may have equal or greater efficacy compared with [CLORAZEPATE](#) for the treatment of adjustment disorders in [breast-cancer](#) patients; [trazodone](#) and [clorazepate](#) had similar safety and tolerability.

b) A small, double-blind pilot study (n=23; efficacy analysis=18) found that a 28-day course of oral [TRAZODONE](#) had equal or greater benefit compared with [CLORAZEPATE](#) for [breast-cancer](#) patients with adjustment disorders (DSM-III-R) accompanied by anxiety or depressed mood and/or mixed disturbance of emotion and conduct [214]. Included were women with a 14 or greater score on the French Hospital Anxiety and Depression Scale (HADS). Enrollees were randomized to oral [trazodone](#) 50 milligrams (mg)/day (n=13) or oral [clorazepate](#) 10 mg/day (n=10), with upward titration of both drugs over 5 days. [Trazodone](#) mean daily dose was 111.5 mg, and [clorazepate](#), mean 17.5 mg. After 28 days, investigator ratings on the Clinical Global Impression (CGI) scale showed that 90.9% of the [trazodone](#) group (10 of 11) and 57.1% of the [clorazepate](#) group (4 of 7) were 'very much improved', 'improved', or 'minimally improved' (p=0.14). Improvement on the Global Severity Index was more pronounced in trazodone-treated patients (-0.68) compared with clorazepate-treated patients (-0.34) (p=0.25). Four adverse events rated as severe occurred in the [trazodone](#) and 5 severe adverse events occurred in the [clorazepate](#) group. One patient receiving [trazodone](#) withdrew due to adverse effects.

4.6.L.2] Adjustment disorder - [HIV infection](#)

a) SUMMARY: [TRAZODONE](#) may be more efficacious than [CLORAZEPATE](#) for the treatment of adjustment disorders in patients with HIV; [trazodone](#) appeared to have greater tolerability.

b) A small, double-blind trial (n=21) found a 28-day course of [TRAZODONE](#) to provide more successful treatment than [CLORAZEPATE](#) for HIV-positive patients with adjustment disorders (DSM-III-R) accompanied by anxiety or depressed mood and/or mixed disturbance of emotion and conduct. Included were patients with a 14 or greater score on the French Hospital Anxiety and Depression Scale (HADS). Enrollees were randomized to oral [trazodone](#) 50 milligrams/day (mg/day) (n=10) or oral [clorazepate](#) 10 mg/day (n=11), with upward titration of both drugs over 5 days. After 28 days, investigator ratings on the Clinical Global Impression (CGI) scale showed that 80% of the [trazodone](#) group and 64% of the [clorazepate](#) group were 'very much improved', 'improved', or 'minimally improved' (p=0.37). Improvements appeared to be more marked in the [trazodone](#) group for depressive symptoms (-0.34 versus -0.09), but slightly more pronounced in the [clorazepate](#) group for anxiety symptoms (-0.32 versus -0.34). At least 1 adverse event occurred in 8 clorazepate-treated patients and 6 trazodone-treated patients. After 2 weeks of treatment, doses were reduced in 1 patient treated with [trazodone](#) and 2 treated with [clorazepate](#) due to adverse effects. More adverse events and a higher number of severe adverse events were associated

with [clorazepate](#) treatment. One patient in each group withdrew due to adverse effects and 1 in each group due to lack of efficacy [215].

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