

DRUGDEX-EV 0073

MICROMEDEX

DRUGDEX® Evaluations  
Database updated July 2015

## **LORAZEPAM**

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

### **0.0] Overview**

#### **1] Class**

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

Antianxiety  
Anticonvulsant  
Skeletal Muscle Relaxant

#### **2] Dosing Information**

##### **a) Adult**

##### **1) [Alcohol withdrawal syndrome](#)**

**a)** 2 mg ORALLY every 6 hr for 4 doses, then 1 mg every 6 hr for 8 doses [1]

##### **2) Anxiety**

**a)** initial, 2 to 3 mg/day ORALLY divided into 2 to 3 daily doses [2] [3]

**b)** maintenance, 2 to 6 mg/day ORALLY divided into 2 to 3 daily doses; dose may vary from 1 to 10 mg/day [2] [3]

##### **3) [Chemotherapy-induced nausea and vomiting](#); Prophylaxis**

**a)** a single dose of 0.025 to 0.05 mg/kg (MAX 4 mg) IM OR IV given slowly (2 mg/min) 30 to 35 min prior to receiving chemotherapy; this dose may be supplemented with oral [lorazepam](#) 1 to 2 mg/hr as needed [5]

##### **4) Insomnia, due to anxiety or situational stress**

a) 2 to 4 mg ORALLY at bedtime [3] [2]

**5) Premedication for anesthetic procedure**

a) 0.05 mg/kg IM (MAX 4 mg) 2 hours before procedure [12]

b) 0.044 mg/kg IV OR 2 mg (whichever is less); MAX dose 0.05 mg/kg IV OR 4 mg (whichever is less) 15 to 20 minutes before the surgical procedure [12]

**6) Sedation**

a) (intermittent) 0.02 to 0.06 mg/kg IV every 2 to 6 hours [41]

b) (continuous infusion) 0.01 to 0.1 mg/kg/hr IV [41]

**7) Status epilepticus**

a) 4 mg IV given slowly at 2 mg/min, may repeat dose in 10 to 15 min if needed; IM dosing may be used, but IV dosing is preferred [12]

**b) Pediatric**

1) (oral) safety and effectiveness of lorazepam tablets in children less than 12 years old have not been established [2] [3]

2) (injection) safety and efficacy has not been established in children less than 18 years old for status epilepticus or preanesthetic sedation [12]

**a) Anxiety**

1) (12 years and older) initial, 2 to 3 mg/day ORALLY divided into 2 to 3 daily doses [2] [3]

2) (12 years and older) maintenance, 2 to 6 mg/day ORALLY divided into 2 to 3 daily doses; dose may vary from 1 to 10 mg/day [2] [3]

**3) Contraindications**

a) hypersensitivity to benzodiazepines or any component of the product (oral and injection) [3] [2] [61] [12], polyethylene glycol, propylene glycol, or benzyl alcohol (injection) [12] [61]

b) intraarterial administration; may produce arteriospasm resulting in gangrene (injection) [12] [61]

c) narrow-angle glaucoma, acute [3] [2] [12] [61]

d) respiratory insufficiency, severe; in the absence of resuscitative equipment (injection) [12] [61]

e) sleep apnea syndrome (injection) [12] [61]

**4) Serious Adverse Effects**

a) [Acidosis](#)

b) [Delirium](#)

**5) Clinical Applications**

**a) FDA Approved Indications**

1) Anxiety

2) Insomnia, due to anxiety or situational stress

3) [Premedication for anesthetic procedure](#)

4) [Status epilepticus](#)

**b) Non-FDA Approved Indications**

1) [Alcohol withdrawal syndrome](#)

2) [Chemotherapy-induced nausea and vomiting](#); Prophylaxis

3) Sedation

**1.0] Dosing Information**

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

**1.1] Drug Properties**

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

**B)** Synonyms

[Lorazepam](#)

**C)** Physicochemical Properties

1) Molecular Weight

a) 321.16 [3] [12] [2]

2) Solubility

a) Almost insoluble in water [3] [12] [2]

**1.2] Storage and Stability**

**A)** Preparation

1) Intramuscular route

a) Inject undiluted solution deep in the muscle mass [12].

**2) Intravenous route**

a) **Lorazepam** injection can be diluted with Sterile Water for Injection, NS, and D5W. Dilute with an equal volume of compatible solution immediately prior to use. Mix thoroughly by gently inverting the container until homogenous, and do not shake vigorously [12].

b) Diluted solution may be injected directly into a vein or into the tubing of an existing **IV infusion**. The rate of injection should not exceed 2 mg/minute [12].

**3) Oral route**

**a) Tablets**

1) When given in divided doses, the largest dose is taken before bedtime [2].

**b) Concentrated Solution**

1) Use only the calibrated dropper provided to measure lorazepam oral solution. Solution can be mixed with liquid or semi-solid food (water, juices, soda or soda-like beverages, applesauce, or puddings) [3].

2) Consume entire mixture immediately, and do not store for future use [3].

**B) Injection route**

**1) Solution**

a) Store under refrigeration and protect from light [12].

**C) Oral route**

**1) Solution/Tablet**

a) Store tablets at controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F). Store in tightly closed bottles [2].

b) Store solution at cold controlled room temperature, between 2 and 8 degrees C (36 and 46 degrees F). Discard opened bottle after 90 days [3].

**D) ADSORPTION**

1) Storage in polyolefin (VISIV, Hospira, Inc.) containers for 24 hours at room temperature did not result in loss of **lorazepam** (0.2 mg/mL in **dextrose 5%**) through **adsorption**. When analyzed by **high-performance liquid chromatography**, the final concentration was 99.6% +/- 0.3% of the initial concentration [280].

2) The **adsorption** of **lorazepam** by flexible polyvinyl **chloride** (PVC) IV tubing and bags is substantially slower than that of **diazepam**. **Lorazepam** is reliably delivered from IV admixtures of **dextrose 5%** in water infused over intervals of up to 5 hours [281]. The stability of **lorazepam 2 mg/mL** (undiluted) was evaluated

in polypropylene infusion-pump syringes. More than 10% lorazepam loss was detected before day 3 of storage [282].

3j) The absorption of lorazepam 40 mg/L in sodium chloride 0.9% was evaluated in glass containers, polyvinylchloride bags, and bags composed of a laminate of polyethylene, nylon, and polypropylene. The containers were stored at 21 degrees C protected from light. In 24 hours, less than 1% lorazepam loss was detected in the glass container, less than 2% loss was detected in the laminate bag, and less than 3% loss was detected in the polyvinylchloride bag [283].

### 1.3] Adult Dosage

#### 1.3.1] Normal Dosage

##### 1.3.1.A] Enteral route

###### 1.3.1.A.1] Sedation

a) In critically ill adults requiring sustained sedation, lorazepam may be administered via an enteral route in tablet or liquid form, although large doses (eg, 60 mg of a 2 mg/mL every 6 hours) may lead to diarrhea due the high polyethylene glycol and propylene glycol content [41].

##### 1.3.1.B] Intramuscular route

###### 1.3.1.B.1] Chemotherapy-induced nausea and vomiting; Prophylaxis

a) A single lorazepam dose of 0.025 to 0.05 mg/kg (maximum, 4 mg) IM is recommended in combination with other antiemetic agents. Lorazepam should be administered approximately 30 to 35 minutes prior to receiving chemotherapy. The initial intramuscular dose may be supplemented with oral lorazepam 1 to 2 mg hourly as needed to maintain mild to moderate sedation [5].

###### 1.3.1.B.2] Premedication for anesthetic procedure

a) The recommended dose for preanesthetic sedation in adults is lorazepam 0.05 mg/kg IM, up to a maximum of 4 mg, 2 hours before the surgical procedure [12] [24] [5].

b) Amnestic effects after IM lorazepam were inferior to similar effects after IV route. The IV or oral route is preferred [25].

###### 1.3.1.B.3] Status epilepticus

a) The IM route is not preferred for status epilepticus since therapeutic lorazepam levels may not be reached as quickly as with intravenous administration . However, should the IV route be unavailable then the IM route may be utilized [12].

##### 1.3.1.C] Intravenous route

###### 1.3.1.C.1] Chemotherapy-induced nausea and vomiting; Prophylaxis

a) A single lorazepam dose of 0.025 to 0.05 mg/kg (maximum, 4 mg) injected slowly intravenously, approximately 30 to 35 minutes prior to receiving chemotherapy is recommended in combination with other antiemetics. The initial intravenous dose may be supplemented with oral lorazepam 1 to 2 mg hourly as needed to maintain mild-to-moderate sedation [5].

###### 1.3.1.C.2] Premedication for anesthetic procedure

a) The recommended dose for preanesthetic sedation in adults is [lorazepam](#) 0.044 mg/kg IV or 2 mg (whichever is less) 15 to 20 minutes before the surgical procedure. Doses up to 0.05 mg/kg IV or 4 mg total may be required in some patients [12].

#### 1.3.1.C.3] Sedation

a) Intermittent

1) The recommended intermittent dose for critically ill adults requiring sustained sedation is 0.02 to 0.06 mg/kg IV every 2 to 6 hours [41].

b) Continuous

1) Because [lorazepam](#) has a half-life of 12 to 15 hours, infusions are not readily titratable so in critically ill adults requiring sustained sedation a loading dose given by IV push should be administered initially, followed by fixed infusion rates. The recommended continuous [IV infusion](#) dose in critically ill adults is 0.01 to 0.1 mg/kg/hr IV. Prolonged high-dose infusions have been associated with reversible [acute tubular necrosis](#), [lactic acidosis](#), and hyperosmolar state due to the presence of solvents ([polyethylene glycol](#) and propylene glycol). An alternative to continuous infusion is undiluted [lorazepam](#) as an infusion using a PCA device [41].

#### 1.3.1.C.4] Status epilepticus

a) For [status epilepticus](#) patients 18 years and older, the recommended dose is 4 mg given slowly at a rate of 2 mg/min. If seizures continue or recur, the dose may be repeated after 10 to 15 minutes. There are limited data regarding further doses [12]

b) The usual recommended dose of [lorazepam](#) is 0.05 to 0.15 mg/kg (maximum, 4 mg) [37], administered at a rate of 2 mg/min for the acute management of [status epilepticus](#). Initial doses may be repeated in 10 to 15 minutes if seizures persist [5]. One large blinded study used [lorazepam](#) 0.1 mg/kg administered at a rate of 2 mg/min [31].

c) The usual maximum [lorazepam](#) dose of 8 mg is based on the subsequent use of loading doses of [phenytoin](#), and if needed [phenobarbital](#). Some clinicians recommend more liberal use of [lorazepam](#) during the initial 24-hour period if seizures persist, resulting in a higher maximum dose [5].

d) [Lorazepam](#) in doses of 4 mg (2 mg/mL solution over 2 minutes) IV was effective in controlling 89% of episodes of [status epilepticus](#) in one controlled study. Corresponding response rates of [diazepam](#) 10 mg over 2 minutes were 76% of episodes [33].

#### 1.3.1.D] Oral route

##### 1.3.1.D.1] Alcohol withdrawal syndrome

a) [Lorazepam](#) 2 mg orally every 6 hours for 4 doses followed 1 mg every 6 hours for 8 doses has been used in a fixed-dose regimen for [alcohol detoxification](#) [1].

##### 1.3.1.D.2] Anxiety

a) The recommended initial dose of [lorazepam](#) is 2 to 3 mg/day orally (divided 2 to 3 times daily). The usual dosage range is 2 to 6 mg daily in divided doses (largest dose at bedtime), but may vary from 1 to 10 mg/day in 2 to 3 divided doses [3] [2].

##### 1.3.1.D.3] Insomnia, due to anxiety or situational stress

a) The recommended dose of [lorazepam](#) for the treatment of insomnia due to anxiety or transient situational stress is 2 to 4 mg orally at bedtime [3] [2].

**1.3.2] Dosage in Renal Failure**

A) Use is not recommended in patients with renal failure. For acute administration in patients with mild to moderate renal impairment no dose adjustment is needed. Use cautiously if frequent doses are given over a relatively short period of time. The administration of the lowest, effective dose is recommended [12].

B) Impaired lorazepam elimination, with an associated prolongation of half-life, occurred following subchronic administration to 2 patients with chronic renal failure [50].

C) No dosage adjustment is necessary for patients with renal failure [51].

**1.3.3] Dosage in Hepatic Insufficiency**

A) Use is not recommended in patients with hepatic failure. No dosage adjustment is needed in patients with mild to moderate renal impairment. The administration of the lowest, effective dose is recommended [12].

B) Dosage adjustment may be required in patients with cirrhosis; however, no specific dosage schedules are available. The changes in lorazepam kinetics in liver disease are not considered significant by some investigators [52].

C) The effect of liver disease on the ability to eliminate lorazepam is variable. The pharmacokinetics of lorazepam were studied in 22 subjects with liver dysfunction [53]. When compared with controls, the metabolic disposition of lorazepam in patients with acute viral hepatitis was unaltered, but in cirrhotic patients the lorazepam half-life was prolonged and plasma protein binding decreased. Altered lorazepam disposition in cirrhotics has been confirmed by other investigators [54] [55]. It was proposed that the decrease in plasma protein binding observed in cirrhotic patients accounted for their increased plasma half-life [54].

**1.3.4] Dosage in Geriatric Patients****A) Oral**

1) Age does not appear to have a clinically significant effect on lorazepam kinetics. However, some elderly individuals may have greater sensitivity (drowsiness, unsteadiness) to lorazepam and therefore, dose selection should be cautious and start at the low end of the dosing range. An initial lorazepam dose of 1 to 2 mg/day in divided doses is recommended and should be adjusted as needed and/or tolerated in order to avoid oversedation [2] [3] [56].

2) The initial lorazepam dose should not exceed 2 mg/day in geriatric patients [57].

**B) Parenteral**

1) Age does not appear to have a clinically significant effect on lorazepam kinetics. However, some elderly individuals may have greater sensitivity (drowsiness, unsteadiness) to lorazepam and therefore, dose selection should be cautious and start at the low end of the dosing range. It is recommended in adults over 50 years of age receiving lorazepam for preanesthetic sedation, that an initial lorazepam dose of 0.044 mg/kg to a total of 2 mg not be exceeded due to prolonged and profound sedative effect [12].

**1.3.5] Dosage Adjustment During Dialysis**

A) No dosage supplementation is necessary following hemodialysis [58].

**1.3.6] Dosage in Other Disease States****A) Debilitated Patients**

1J) For debilitated patients, an initial oral lorazepam dose of 1 to 2 mg/day, in divided doses is recommended and may be adjusted as needed and/or tolerated [2] [3].

**BJ) Obese Patients**

1J) The dose of lorazepam should be increased in proportion to total body weight in obese patients, due to an increase in volume of distribution in direct proportion to total body weight [59].

**CJ) Spinal Cord Injuries**

1J) The pathophysiology of spinal cord injuries does not appear to influence the disposition of lorazepam; therefore, no dosage adjustment is necessary [60].

**1.4J Pediatric Dosage**

**1.4.1J Normal Dosage**

**1.4.1.AJ Intramuscular route**

1J) Pediatric patients may exhibit a sensitivity to benzyl alcohol, polyethylene glycol and propylene glycol components of lorazepam injection [12].

**2J) Status Epilepticus**

aJ) Safety of lorazepam injection have not been established in children less than 18 years old for the treatment of status epilepticus [12].

**3J) Preanesthetic Sedation**

aJ) There is insufficient data to support efficacy or to make dosage recommendations for preanesthetic sedation in children less than 18 years of age [12].

**1.4.1.BJ Intravenous route**

**1.4.1.B.1J Chemotherapy-induced nausea and vomiting; Prophylaxis**

aJ) Lorazepam 0.05 mg/kg (maximum, 2 mg) was effective in controlling chemotherapy-induced nausea and vomiting in children 2 to 15 years of age in an uncontrolled pilot study. Lorazepam was administered intravenously over 20 minutes, 30 minutes prior to chemotherapy with agents producing moderate emetic effects (doxorubicin, dactinomycin, cyclophosphamide, ifosfamide, mechlorethamine, intrathecal methotrexate, cytarabine) [30].

1.4.1.B.2J) Pediatric patients may exhibit a sensitivity to benzyl alcohol, polyethylene glycol and propylene glycol components of lorazepam injection. In neonates, IV administration of high levels of benzyl alcohol has been associated with gasping syndrome characterized by CNS depression and toxicity, metabolic acidosis, and gasping respirations [12].

**1.4.1.B.3J) Status Epilepticus**

aJ) Safety of lorazepam injection has not been established in children less than 18 years old for the treatment of status epilepticus [12].

**1.4.1.B.4J) Preanesthetic Sedation**

aJ) There is insufficient data to support efficacy or to make dosage recommendations for preanesthetic sedation in children less than 18 years of age [12].

**1.4.1.CJ Oral route**



**1.4.1.C.1] Anxiety**

a) The recommended initial dose of [lorazepam](#) for children 12 years and older is 2 to 3 mg/day orally (divided 2 to 3 times daily). The usual dosage range is 2 to 6 mg daily in divided doses (largest dose at bedtime), but may vary from 1 to 10 mg/day in 2 to 3 divided doses [3] [2].

**1.4.1.C.2] Insomnia, due to anxiety or situational stress**

a) The recommended dose of insomnia due to anxiety or transient situational stress for children 12 years and older is 2 to 4 mg orally at bedtime [3] [2].

**1.4.1.C.3)] Safety and effectiveness of [lorazepam](#) tablets in children less than 12 years old have not been established [2].**

**1.4.1.D] Sedation**

See Drug Consult reference: PEDIATRIC SEDATION REGIMENS

**1.4.2] Dosage in [Renal Failure](#)**

A) No dosage adjustment is necessary for patients with [renal failure](#) [51].

**1.4.3] Dosage in [Hepatic Insufficiency](#)**

A) Dosage adjustment may be required in patients with [cirrhosis](#); however, no specific dosage schedules are available. The changes in [lorazepam](#) kinetics in liver disease are not considered significant by some investigators [52].

B) The effect of liver disease on the ability to eliminate [lorazepam](#) is variable. The pharmacokinetics of [lorazepam](#) were studied in 22 subjects with [liver dysfunction](#) [53]. When compared with controls, the metabolic disposition of [lorazepam](#) in patients with acute [viral hepatitis](#) was unaltered, but in cirrhotic patients the [lorazepam](#) half-life was prolonged and plasma protein binding decreased. Altered [lorazepam](#) disposition in cirrhotics has been confirmed by other investigators [54] [55]. The decrease in plasma protein binding observed in cirrhotic patients accounts for their increased plasma half-life [24] [54].

**1.4.4] Dosage Adjustment During Dialysis**

A) No dosage supplementation is necessary following [hemodialysis](#) [58].

**2.0] Pharmacokinetics**

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

**2.1] Onset and Duration**

A) Onset

1) Initial Response

a) Hypnotic, oral: 20 to 30 minutes [250].

b) In some cases, [LORAZEPAM](#) sublingual formulation administered by the SUBLINGUAL route may result in a faster onset of therapeutic effect than orally administered [lorazepam](#).

Sublingual administration of [lorazepam](#) also compares favorably in time to onset with [intramuscular injection](#) of the drug [251] [252] [253].

## 2)) Peak Response

- a)) Amnesic effects, oral: 60 to 90 minutes [254].
- b)) Amnesic effects, intramuscular: 2 hours [224].
- c)) Amnesic effects, intravenous: 15 to 20 minutes [224].

## B)) Duration

### 1)) Single Dose

- a)) Hypnotic, oral: 6 to 8 hours [250] [255].
- b)) Amnesic effects, intramuscular: 6 to 8 hours [224].
- c)) Amnesic effects, intravenous: 6 to 8 hours [224].
- d)) [Status epilepticus](#): 3 to 6 hours [256].

1)) Duration is not dose-related [256].

## 2.2) Drug Concentration Levels

### A)) Peak Concentration

1)) IV, single-dose, 0.05 mg/kg, pediatrics: 56.1 nanograms/mL [257]

- a)) In a prospective, multicenter [pharmacokinetic study](#) that included pediatric patients (5 months to 17 years of age) with a history of [status epilepticus](#) (n=15), mean C<sub>max</sub> after a single [lorazepam](#) dose of 0.05 mg/kg (maximum, 2 mg) slow IV push over 1 minute was 56.1 +/- 44.9 nanograms/mL (range, 29.3 to 209.6 nanograms/mL) [258].

### B)) Time to Peak Concentration

1)) Oral: 2 hours (range 0.5 to 3 hours) [259] [260] [261].

- a)) Secondary higher peaks may occur at 1 to 5 hours [260].

2)) Intramuscular: 1 to 3 hours [224] [261].

3)) Sublingual: 60 minutes [262].

### C)) Area Under the Curve

1)) IV, single-dose, 0.05 mg/kg, pediatrics: 822.5 nanograms x hr/mL [257]

- a)) In a prospective, multicenter [pharmacokinetic study](#) that included pediatric patients (5 months to 17 years of age) with a history of [status epilepticus](#) (n=15), mean AUC (0 to infinity) after a single

lorazepam dose of 0.05 mg/kg (maximum, 2 mg) slow IV push over 1 minute was 822.5 +/- 706.1 nanograms x hr/mL (range, 253.3 to 3202.5 nanograms x hr/mL) [258].

## 2.3] ADME

### 2.3.1] Absorption

#### A)] Bioavailability

1)] Oral: 90% to 93% [259] [260] [263].

2)] Intramuscular: 83% to 100% [261].

3)] Comparing SUBLINGUAL and ORAL lorazepam formulations after multiple dosing, it was concluded that the sublingual tablet had similar steady state concentrations, the same bioavailability, and a faster absorption rate compared to orally administered lorazepam. Bioavailability of the oral tablet was greater when the tablet was administered orally as compared to sublingually [251] [252] [253].

### 2.3.2] Distribution

#### A)] Distribution Sites

##### 1)] Protein Binding

a)] 85% to 91% [224] [260] [263].

1)] The free fraction was significantly higher in elderly patients [267].

##### 2)] OTHER DISTRIBUTION SITES

a)] CEREBROSPINAL FLUID [261].

1)] CSF levels averaged 5% to 28% of serum levels (Aaltonen et al, 1980, Ochs et al, 1980).

b)] PLACENTA

1)] Plasma levels in newborns approximate those in maternal serum [261].

#### B)] Distribution Kinetics

##### 1)] Distribution Half-Life

a)] 20 to 25 minutes (10.3 to 42.7, range) (Reynolds, 1991, Greenblatt et al, 1979c).

##### 2)] Volume of Distribution

a)] 1.3 L/kg [224] [263].

1) The intravenous volume of distribution was significantly reduced in elderly patients [268].

b) Pediatrics: 1.48 L/kg [257]

1) In a prospective, multicenter pharmacokinetic study (n=63) of pediatric patients (median age, 7 years, 2 months; range, 5 months to 17 years) treated for status epilepticus (SE) or with a history of SE, the mean Vd was 1.48 +/- 0.54 L/kg. Mean Vd was 1.62 +/- 0.59 L/kg in subjects 3 months to less than 3 years old, 1.5 +/- 0.61 L/kg in subjects 3 years to less than 13 years old, and 1.27 +/- 0.17 L/kg in subjects 13 years to less than 18 years old. Lorazepam was administered slow IV push over 1 minute. Subjects treated for SE (n=48) received lorazepam 0.05 to 0.1 mg/kg (exact dose was decision of treating physician) to a maximum of 4 mg; additional treatment for SE, including additional doses of lorazepam, was allowed. Subjects with a history of SE (n=15) received a single dose of lorazepam 0.05 mg/kg to a maximum of 2 mg and had a mean Vd of 1.92 +/- 0.85 L/kg [258].

### 2.3.3] Metabolism

#### A) Metabolism Sites and Kinetics

1) LIVER, 75% [263].

a) Chronic dosing has no effect on hepatic hydroxylation capacity [269].

b) Undergoes enterohepatic recirculation [224].

#### B) Metabolites

1) 3-O-phenolic glucuronide, inactive [224] [259].

a) Approximately 75% is converted to the glucuronide derivative [263] [260].

2) 6-chloro-4-O-chlorophenyl-2, 1-quinazolinone, and the hydroxylated derivative of **LORAZEPAM**, inactive [270] [271].

### 2.3.4] Excretion

#### A) Kidney

1) Renal Excretion (%)

a) 88% [224].

2) FECES, 7% [224].

#### B) Total Body Clearance

1) 1.1 mL/min/kg [224].

2) Pediatrics: 1.2 mL/min/kg [257]

a) In a prospective, multicenter [pharmacokinetic study](#) (n=63) of pediatric patients (median age, 7 years, 2 months; range, 5 months to 17 years) treated for [status epilepticus](#) (SE) or with a history of SE, the mean total body clearance was 1.2 +/- 0.93 mL/min/kg. Mean total body clearance was 1.57 +/- 1.62 mL/min/kg in subjects 3 months to less than 3 years old (n=18), 1.12 +/- 0.4 mL/min/kg in subjects 3 years to less than 13 years old (n=29), and 0.95 +/- 0.32 mL/min/kg in subjects 13 years to less than 18 years old (n=16). [Lorazepam](#) was administered slow IV push over 1 minute. Subjects treated for SE (n=48) received [lorazepam](#) 0.05 to 0.1 mg/kg (exact dose was decision of treating physician) to a maximum of 4 mg; additional treatment for SE, including additional doses of [lorazepam](#), was allowed. Subjects with a history of SE (n=15) received a single dose of [lorazepam](#) 0.05 mg/kg to a maximum of 2 mg and had a mean total body clearance of 49.33 +/- 30.83 mL/min/kg [258].

### 2.3.5] Elimination Half-life

#### A) Parent Compound

1) 12 hours [259].

a) The half-life in newborn infants is 3 to 4 times that of adults [260] [273].

2) Pediatrics: 16.8 hours [257]

a) In a prospective, multicenter [pharmacokinetic study](#) (n=63) of pediatric patients (median age, 7 years, 2 months; range, 5 months to 17 years) treated for [status epilepticus](#) (SE) or with a history of SE, the mean terminal t(1/2) was 16.8 +/- 7.1 hours. Mean t(1/2) was 15.8 +/- 6.5 hours in subjects 3 months to less than 3 years old (n=18), 16.9 +/- 7.4 hours in subjects 3 years to less than 13 years old (n=29), and 17.8 +/- 7.7 hours in subjects 13 years to less than 18 years old (n=16). [Lorazepam](#) was administered slow IV push over 1 minute. Subjects treated for SE (n=48) received [lorazepam](#) 0.05 to 0.1 mg/kg (exact dose was decision of treating physician) to a maximum of 4 mg; additional treatment for SE, including additional doses of [lorazepam](#), was allowed. Subjects with a history of SE (n=15) received a single dose of [lorazepam](#) 0.05 mg/kg to a maximum of 2 mg and had a mean t(1/2) of 20.5 +/- 10.2 hours [258].

#### B) Metabolites

1) 3-0-phenolic glucuronide, 12 to 18 hours [224] [259] [260] [274].

### 2.3.6] Extracorporeal Elimination

#### A) Hemodialysis

1) Dialyzable: Yes

a) The unbound fraction of the conjugate [lorazepam](#) glucuronide is reported to be dialyzable [271].

## 3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)[Drug Interactions](#)**3.1] Contraindications**

- A) hypersensitivity to benzodiazepines or any component of the product (oral and injection) [3] [2] [61] [12], [polyethylene glycol](#), propylene glycol, or benzyl alcohol (injection) [12] [61]
- B) [intraarterial administration](#); may produce [arteriospasm](#) resulting in [gangrene](#) (injection) [12] [61]
- C) [narrow-angle glaucoma](#), acute [3] [2] [12] [61]
- D) [respiratory insufficiency](#), severe; in the absence of resuscitative equipment (injection) [12] [61]
- E) [sleep apnea syndrome](#) (injection) [12] [61]

**3.2] Precautions**

- A) abrupt discontinuation; may result in withdrawal symptoms or in exacerbation of symptoms (oral) [2] [3]
- B) concomitant [anesthesia](#); risk of heavy sedation and possible [airway obstruction](#) (injection) [12] [61]
- C) concomitant CNS depressant and alcohol use; increased risk of potentially fatal [respiratory depression](#) [2] [3] [12] [61]
- D) concomitant use of medications that lower the convulsive threshold (such as antidepressants); increased risk of convulsions/seizures if [lorazepam](#) is abruptly withdrawn (oral) [2] [3]
- E) debilitated patients; increased risk of [hypoventilation](#), or hypoxic [cardiac arrest](#) (injection) [12] [61]; and increased risk of sedation (oral); initial oral dose should not exceed 2 mg, monitoring recommended, consider dose adjustment [2] [3]
- F) [depressive disorder](#), primary or [psychosis](#); suicide potential or exacerbation of depression; use not recommended (oral) [2] [3]
- G) drug or alcohol abuse, history; increased risk of drug abuse and dependence; monitoring recommended (oral) [2] [3]
- H) elderly patients; increased risk of [hypoventilation](#), or hypoxic [cardiac arrest](#) (injection) [12] [61]; and increased risk of sedation (oral); initial oral dose should not exceed 2 mg, monitoring recommended, consider dose adjustment [2] [3]
- I) [hepatic failure](#); not recommended (injection) [12] [61]
- J) [hepatic insufficiency](#), severe and/or [encephalopathy](#); risk of worsening [encephalopathy](#); consider dose adjustments (oral) [2] [3]
- K) higher doses; increased risk of propylene glycol toxicity or [polyethylene glycol](#) toxicity especially in patients with [renal impairment](#) (injection) [12] [61]
- L) multiple doses; increased risk of impaired consciousness (injection) [12] [61]
- M) neonate patients; increased risk of fatal "gasping syndrome" due to benzyl alcohol, especially with higher doses (injection) [12] [61]
- N) paradoxical reactions have been reported [2] [3] [12] [61]
- O) patients over 50 years of age; increased risk of profound and prolonged sedation (injection) [12] [61]
- P) pediatric patients; increased incidence of sensitivity to benzyl alcohol, [polyethylene glycol](#), and propylene glycol especially in high doses (injection) [12] [61]
- Q) personality disorders, significant; increased risk of drug dependence (oral) [2] [3]
- R) physical and psychologic dependence may occur; risk increases with higher doses and prolonged use; not recommended for long-term use (oral) [2] [3]
- S) premature and low-birth-weight infants; seizure activity and myoclonus have been reported (injection) [12] [61]
- T) pulmonary reserve, limited; risk of [hypoventilation](#) or hypoxic [cardiac arrest](#) (injection) [12] [61]
- U) [renal failure](#); not recommended (injection) [12] [61]

- V) respiratory function, compromised ([sleep apnea syndrome](#) and [chronic obstructive pulmonary disease](#)); increased risk of [respiratory depression](#) (oral) [2] [3]
- W) sedated patients, heavily; increased risk for [airway obstruction](#) (injection) [12] [61]
- X) seizure disorder, increased risk of convulsions/seizures if [lorazepam](#) is abruptly withdrawn (oral) [2] [3]
- Y) [status epilepticus](#); risk of [respiratory depression](#); monitoring recommended (injection) [12] [61]

### 3.3] Adverse Reactions

#### 3.3.1] Cardiovascular Effects

##### 3.3.1.A] Hypertension

- 1) Incidence: 0.1% [63]
- 2) [Hypertension](#) (0.1%) has been reported occasionally following [parenteral administration](#) of [lorazepam](#) [63].

##### 3.3.1.B] Hypotension

- 1) Incidence: 0.1% to 2.4% [63].
- 2) Hypotension has been observed occasionally (0.1%) among patients receiving injectable [lorazepam](#), however hypotension was observed in 1.5% to 2.4% of patients receiving injectable [lorazepam](#) in [status epilepticus](#) clinical trials. [63].
- 3) Small, but clinically insignificant reductions in blood pressure have occurred following oral administration of [lorazepam](#) [62].

#### 3.3.2] Dermatologic Effects

##### 3.3.2.A] Dermatological finding

See Drug Consult reference: NONCYTOTOXIC [DRUG EXTRAVASATION THERAPY](#)

##### 3.3.2.B] Erythema

- 1) Redness at the injection site following IM administration of [lorazepam](#) occurred in approximately 2% of patients. Twenty-four hours later, redness persisted in 0.8% of patients (n=859) [63].

##### 3.3.2.C] Injection site pain

- 1) With [intramuscular injection](#), the incidence of injection site pain and burning was 17% during the immediate post-injection period and about 1.4% at the 24-hour observation time. Redness occurred in 2% of patients [63].
- 2) With intravenous administration, pain and burning occurred in 1.6% during the immediate post-injection period and in 0.5% after 24 hours [63].

##### 3.3.2.D] Rash

- 1) A skin rash has occasionally developed in patients who have received [lorazepam](#) parenterally in combination with other drugs during [anesthesia](#) [63].

#### 3.3.3] Endocrine/Metabolic Effects

##### 3.3.3.A] Acidosis

- 1) Incidence: less than 1% [63]

2) **Acidosis** has been reported in less than 1% of patients receiving injectable **lorazepam** in a dose-comparison trial (n=130) [63].

3) In a prospective observational study, six out of nine critically ill adult patients had evidence of hyperosmolar, high anion gap **metabolic acidosis** consistent with propylene glycol accumulation while on high dose continuous **lorazepam** infusions (at least 10 mg/hr). All patients had elevated **osmolal gaps** at 48 hours after continuous infusion of high dose **lorazepam**. The strength of the relationship between the rising **osmolal gap** and propylene glycol serum concentrations at 48 hours was strong ( $r=0.804$ ,  $p=0.001$ ). The study also reported a significant correlation between the continuous infusions of high dose **lorazepam** and propylene glycol serum concentrations ( $r=0.481$ ,  $p=0.038$ ) and between the high dose **lorazepam** infusion rate and propylene glycol serum concentrations ( $r=0.557$ ,  $p=0.021$ ). The study included patients that were on high dose **lorazepam** (greater than or equal to 10 mg/hr) for a minimum of 48 hours. Patients were monitored for cumulative **lorazepam** received (mg/kg) and rate of infusion (mg/kg/hr) from the start of the high dose continuous infusion of **lorazepam** until 24 hours after the infusion stopped, however no significant correlation was found between propylene glycol serum concentrations and the duration of **lorazepam** infusion as well as the cumulative non-high-dose **lorazepam** dose in milligram per kilogram (mg/kg) received. The admitting diagnosis of the included patients were as follows, acute respiratory failure (n=7), **septic shock** (n=1), and **fatty liver of pregnancy** (n=1). The minimum **creatinine clearance** at baseline was 50 mL/min (range 50 mL/min to 100 mL/min). High anion gap **metabolic acidosis** in association with intravenous **lorazepam** is most commonly reported in patients receiving higher than recommended doses [77].

4) Retrospective chart review revealed **metabolic acidosis** in 8 patients who had rising serum creatine concentrations while on continuous **lorazepam** infusion. The magnitude of the rise showed a weak-to-moderate correlation ( $r=0.53$ ) with propylene glycol concentration (mean propylene glycol at the time of peak serum **creatinine** concentration was 1103 micrograms/milliliter) [78].

5) As part of treatment for acute respiratory failure resulting from Escherichia coli sepsis and **pneumonia**, **lorazepam** appeared to have contributed to the worsening of **metabolic acidosis**. Initial laboratory tests of a 34-year-old woman who presented with acute respiratory failure showed metabolic anion-gap **acidosis**, with normal blood sugar and no ketones. After 4 days of treatment, the **acidosis** was more extreme, with greatly increased serum osmolality and an **osmolal gap** of 165 milliosmoles per liter (mOsm/L). The woman was being sedated with intravenous **lorazepam**, up to 30 milligrams per hour, which contained **polyethylene glycol-400** (PEG-400) in propylene glycol with 2% benzyl alcohol. In 78 hours she had received a cumulative dose of 1696 mg of **lorazepam** and 153 milliliters of PEG-400. After 3 sessions of **hemodialysis**, her pH and bicarbonate level improved and her **osmolal gap** decreased to 40 mOsm/L. She was discharged after 26 days in the hospital with stable renal function [79]. PEG, oxidized by alcohol dehydrogenase to hydroxy acid and acid metabolites, may have contributed to the **acidosis**.

### 3.3.3.B] Hyperosmolarity

1) A 15-year-old boy receiving a continuous infusion of **lorazepam** and **morphine** developed hyperosmolarity and hypotension increased requirements for transfusions, and bilateral **knee effusions**. Propylene glycol in the **lorazepam** infusion was suspected and **lorazepam** was replaced by **midazolam**. The hyperosmolarity resolved within 24 hours. The need for vasopressor therapy and transfusions decreased and **knee effusions** resolved over the next few days [80].

### 3.3.3.C] Hyponatremia

1) **Hyponatremia** has been reported with benzodiazepines, including **lorazepam** [3].

### 3.3.3.D] Syndrome of inappropriate antidiuretic hormone secretion



- 1) Syndrome of inappropriate diuretic hormone secretion has been reported with benzodiazepines, including [lorazepam](#) [3].

### 3.3.4] Gastrointestinal Effects

#### 3.3.4.A] Nausea and vomiting

- 1) Incidence: less than 1% [63]
- 2) Nausea and vomiting have been reported infrequently (less than 1%) in patients who have received [lorazepam](#) parenterally (n=326). Nausea and vomiting have occasionally been reported in patients receiving injectable [lorazepam](#) in combination with other drugs during [anesthesia](#) [63].
- 3) Nausea has been reported following treatment with benzodiazepines, including [lorazepam](#) [62].

### 3.3.5] Hematologic Effects

#### 3.3.5.A] Agranulocytosis

- 1) [Agranulocytosis](#) has been reported in patients receiving benzodiazepines, including [lorazepam](#) [3] [62].

#### 3.3.5.B] Leukopenia

- 1) [Leukopenia](#) has been associated with [lorazepam](#) in a few patients [62]. Periodic blood counts are recommended for patients on long-term therapy [3].

#### 3.3.5.C] Thrombocytopenia

- 1) [Thrombocytopenia](#) has been reported in patients receiving benzodiazepines, including [lorazepam](#) [3] [62].

### 3.3.6] Hepatic Effects

#### 3.3.6.A] Increased liver function test

- 1) Increases in [bilirubin](#), transaminases and [alkaline phosphatases](#) have been reported following treatment with benzodiazepines, including [lorazepam](#) [3].
- 2) A series of 5 patients received [lorazepam](#) 2 mg/day for 7 days and demonstrated no change in liver function. However, when [lorazepam](#) was taken with [pyrimethamine](#), a significant increase in BSP, [bilirubin](#) and transaminase occurred [81].
- 3) Elevations in lactic dehydrogenase ([LDH](#)) have occurred in a few patients receiving long-term [lorazepam](#) therapy. Liver functions tests should be performed periodically in patients receiving [lorazepam](#) long-term [62].

#### 3.3.6.B] Jaundice

- 1) [Jaundice](#) has been reported following treatment with benzodiazepines, including [lorazepam](#) [3] [62].

### 3.3.7] Immunologic Effects

#### 3.3.7.A] Anaphylaxis

- 1) Anaphylactic/[anaphylactoid reactions](#) have been reported following treatment with benzodiazepines, including [lorazepam](#) [3].

#### 3.3.7.B] Hypersensitivity reaction

1J) [Hypersensitivity reactions](#) and allergic skin reactions have been reported following treatment with benzodiazepines, including [lorazepam](#) [3].

### 3.3.9] Neurologic Effects

#### 3.3.9.A] [Akathisia](#)

1J) [Akathisia](#) developed in 1 patient who received an antiemetic regimen that included [metoclopramide](#), [dexamethasone](#), [diphenhydramine](#), and [lorazepam](#) prior to cisplatin administration [69].

#### 3.3.9.B] [Asthenia](#)

1J) Incidence: 4.2% [3] [62]

2J) Among 3,500 patients treated for anxiety, weakness was reported in 4.2% of patients receiving [lorazepam](#) [3] [62].

#### 3.3.9.C] [Dizziness](#)

1J) Incidence: 6.9% [3] [62]

2J) Among 3,500 patients treated for anxiety, dizziness was reported in 6.9% of patients receiving [lorazepam](#) [3] [62].

#### 3.3.9.D] [Dyskinesia](#)

1J) [Orofacial dyskinesias](#) developed in a 60-year-old woman following [lorazepam](#) 3 mg PO TID for approximately 2 weeks. Withdrawal of the drug resulted in resolution of [dyskinesias](#) within approximately 1 month. Several months later, [lorazepam](#) 1.5 mg TID was given with [propranolol](#) 120 mg daily resulting in recurrence of [dyskinesias](#). The patient was free of [dyskinesias](#) during a previous course of [propranolol](#) therapy. The patient was receiving sulpiride when [dyskinesias](#) occurred and had taken numerous psychoactive agents ([doxepin](#), [amitriptyline](#)), over the previous 3 years which may have contributed to the occurrence of [dyskinesias](#) when [lorazepam](#) therapy was initiated [66].

#### 3.3.9.E] [Extrapyramidal sign](#)

1J) Extrapyramidal symptoms have been reported with benzodiazepines, including [lorazepam](#) [3].

#### 3.3.9.F] [Headache](#)

1J) Headache has been reported in patients receiving benzodiazepines, including [lorazepam](#) [62].

#### 3.3.9.G] [Memory impairment](#), [Transient](#)

1J) [Transient amnesia](#) or [memory impairment](#) has been associated with administration of benzodiazepines, including [lorazepam](#) [62] [73].

2J) Three subjects experienced [anterograde amnesia](#) during the day after the first drug night. Similar findings were reported with [lorazepam](#) 3 mg at bedtime [65].

#### 3.3.9.H] [Sedated](#)

1J) Incidence: 15.9% [3] [62]

2J) Among 3,500 patients treated for anxiety, sedation was reported in 15.9% of patients receiving [lorazepam](#). Incidence of sedation increased with age [3] [62]. The sedation appeared to be dose-related [71], and can significantly affect hand-eye coordination [72].

3J) Elderly and debilitated patients may be more susceptible to the sedative effects of lorazepam. These patients should be monitored frequently and their dosages adjusted according to patient response. Initial dosage in these cases should not exceed 2 mg [3].

### 3.3.9.I] Seizure

#### 1J) Summary

- aJ) Seizures have occurred and are possible during use of lorazepam or other benzodiazepines, although they may be more common in patients with preexisting seizure disorders or in those patients taking concomitant medications that lower the seizure threshold [3].
- 2J) Two cases of full-term infants receiving lorazepam and subsequently having seizure-like activity were reported [67]. A 2940 gram male was born with severe transient tachypnea of the newborn. At 3 hours the infant was intubated for progressive symptoms of transient tachypnea and was given lorazepam 0.1 mg/kg IV. Within minutes, the infant had nonsuppressible clonic jerks of both legs and the right upper extremity. These occurred in bursts that lasted 1 to 3 minutes and recurred over 1 hour. In the second case, a 2977 gram male initially required oxygen and had tachypnea. At 72 hours, the infant started treatment for necrotizing enterocolitis, mild abdominal tenderness, and pneumatosis intestinalis. On day 10, lorazepam 0.1 mg/kg IV was given as a sedative prior to placing a percutaneous central catheter for IV access. The infant then experienced intermittent clonic movements of all extremities lasting 1 to 2 minutes, followed by flaccidity and pallor which resolved in 5 minutes. Clonic episodes recurred approximately every 5 minutes for the next 30 minutes and then resolved. Both children had normal physical examinations at 12 months of age.
- 3J) Lorazepam 1.5 mg IV was associated with tonic seizures when given for the treatment of atypical absence status epilepticus in a 10-year-old girl with Lennox-Gastaut syndrome. The seizure lasted less than 2 minutes without the occurrence of cardiac or respiratory compromise. The patient was receiving phenobarbital and valproic acid prior to the occurrence of absence status, and an increase in valproic acid resulted in gradual improvement of clinical status and EEG over several days. The patient subsequently received clorazepate orally without adverse effects. This case report suggests that lorazepam is capable of precipitating tonic seizures in patients with Lennox-Gastaut syndrome [68].

### 3.3.9.J] Sleep disorder

1J) Rebound insomnia has occurred following prolonged use of lorazepam 4 mg as a nighttime sedative; these effects were accompanied by increased tension, anxiety, and panic during the daytime. In this study, performance decrements during the daytime occurred (hangover effects and varying degrees of impaired functioning), primarily during the first several days of nighttime therapy [64]. Three subjects also experienced anterograde amnesia during the day after the first drug night. Similar findings were reported with lorazepam 3 mg at bedtime [65].

### 3.3.9.K] Somnolence

- 1J) Drowsiness has been reported following treatment with benzodiazepines, including lorazepam [62].
- 2J) Lorazepam 0.05 mg/kg IM as a preanesthetic medication for various neurosurgical procedures produced excessively prolonged drowsiness in several patients after surgery [70]. These investigators do not recommend the use of lorazepam as premedication for neurosurgical patients, due to difficulty in evaluating postoperative neurological status.

See Drug Consult reference: ANTIHISTAMINE IMPAIRMENT OF DRIVING

### 3.3.9.L] Summary

1J) Sedation, dizziness, vertigo, weakness, and unsteadiness have been reported following use of lorazepam. Central nervous system effects are dose dependent, with more severe effects occurring with high doses [3].

Less frequent side effects associated with lorazepam include disorientation, depression, headache, sleep disturbances, agitation, restlessness, confusion, and delirium [76].

#### 3.3.9.M] Unsteadiness present

- 1) Incidence: 3.4% [3] [62]
- 2) Among 3,500 patients treated for anxiety, unsteadiness was reported in 3.4% of patients receiving lorazepam. Incidence of unsteadiness increased with age [3] [62].

#### 3.3.9.N] Vertigo

- 1) Vertigo has been reported following usual therapeutic doses of lorazepam [62] [74] [75].

### 3.3.10] Ophthalmic Effects

#### 3.3.10.A] Raised intraocular pressure

- 1) Lorazepam use is contraindicated in patients with acute narrow-angle glaucoma [3] [62] [63].
- 2) Any drug with anticholinergic activity has the propensity to exacerbate narrow angle glaucoma by causing mydriasis of the pupil. According to animal data, benzodiazepines possess some anticholinergic properties so the potential for anticholinergic side effects resulting from the use of benzodiazepines in humans may exist. Therefore, there is a warning in the package insert about use of benzodiazepines in patients who have or are at risk for narrow angle glaucoma [82] [83]; (Hayms & Kuob, 1977) [84].
- 3) A series of 17 patients with glaucoma received lorazepam 1 to 2 mg/day orally for greater than 3 months to determine the effect on intraocular pressure. Lorazepam did not affect intraocular pressure. No anticholinergic or other adverse effects were noted and the authors stated that lorazepam can be used safely in patients with glaucoma (Calixto & deCosta, 1975).

#### 3.3.10.B] Visual disturbance

- 1) Visual disturbance, including diplopia and blurred vision, have been reported with benzodiazepines, including lorazepam [62].

### 3.3.11] Otic Effects

#### 3.3.11.A] Ototoxicity

- 1) Depressed hearing has been infrequently reported during the peak-effect period of lorazepam [63].
- 2) Tinnitus has been reported associated with drug withdrawal [89].

### 3.3.12] Psychiatric Effects

#### 3.3.12.A] Catatonia

- 1) A 62-year-old man with a history of schizophrenia developed withdrawal symptoms and then manifested catatonia 4 days after lorazepam was tapered and discontinued. Lorazepam 0.5 mg was administered intramuscularly and 2 hours later the patient was up and verbalizing his needs. Lorazepam 0.5 mg twice daily was restarted [88].

#### 3.3.12.B] Delirium

- 1) There is an increased risk of daily transitioning to delirium with lorazepam use in the intensive care unit (ICU) according to a cohort analysis of mechanically ventilated ICU patients (n=198) admitted to a university hospital over a 15-month period. In the multivariable analysis, risk of transitioning to delirium

increased with each unit dose of lorazepam given in the previous 24 hours (adjusted odds ratio (OR), 1.2; 95% confidence interval (CI), 1.1 to 1.4; p=0.003). Risk also increased with severity of illness based on each additional APACHE II score (adjusted OR, 1.06; 95% CI, 1.02 to 1.11; p=0.004), and was associated with each year of advancing age (adjusted OR, 1.02; 95% CI, 1 to 1.03; p=0.04) [85].

### 3.3.12.C] Depression

1) Depression has been reported following treatment with benzodiazepines, including lorazepam. Depression may also occur following abrupt discontinuation of lorazepam [86].

2) Lorazepam may unmask a depressive disorder. Preexisting depression may emerge or worsen during use of lorazepam or other benzodiazepines. Lorazepam is not recommended for patients with a primary depressive disorder or psychosis [3].

### 3.3.12.D] Hallucinations

1) Hallucinations may occur in patients during treatment with or following abrupt discontinuation of lorazepam [86].

2) An unusual case of musical hallucinations in an elderly woman with preexisting tinnitus was reported following initiation of unspecified doses of lorazepam as an anxiolytic and temazepam as a hypnotic. The hallucinations consisted of popular songs and hymns and were associated with hyperacusis. Hallucination intensity was reduced following discontinuation of temazepam and dosage reduction of lorazepam; all symptoms disappeared following substitution with chloral hydrate [87].

### 3.3.12.E] Psychotic disorder, Paradoxical

1) Paradoxical reactions have occasionally been reported with benzodiazepine use and may occur with lorazepam. Such reactions may be more likely to occur in children and the elderly and may include anxiety, excitation, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, and hallucinations. Should these occur, lorazepam should be discontinued [3].

### 3.3.12.F] Suicidal thoughts

1) In patients with depression, a possibility for suicide exists. Benzodiazepines should not be prescribed in such patients without adequate antidepressant therapy [3].

## 3.3.13] Renal Effects

### 3.3.13.A] Serum creatinine raised

1) Retrospective chart review revealed metabolic acidosis in 8 patients who had rising serum creatine concentrations while on continuous lorazepam infusion. The magnitude of the rise showed a weak-to-moderate correlation (r=0.53) with propylene glycol concentration (mean propylene glycol at the time of peak serum creatinine concentration was 1103 mcg/mL) [78].

## 3.3.15] Respiratory Effects

### 3.3.15.A] Apnea

1) Apnea and worsening of sleep apnea have been reported following treatment with benzodiazepines, including lorazepam [3].

### 3.3.15.B] Respiratory depression

- 1) Administration of benzodiazepines, including [lorazepam](#), may result in potentially fatal [respiratory depression](#), when used alone or in combination with other CNS depressants. [Respiratory depression](#) is dose dependent with more severe effects occurring with high doses. Additionally, [lorazepam](#) should be used with caution in patients with impaired respiratory function, as the drug has been reported to worsen [obstructive pulmonary disease](#) [3].
- 2) In rare cases (5/446 patients), partial [airway obstruction](#) has developed, which was thought to be due to excessive sleepiness and resulted in temporary underventilation. Patients also received [regional anesthesia](#). When [lorazepam](#) is administered at higher than recommended doses or at the recommended dose, heavy sedation may result. Therefore the necessary equipment to maintain a patent airway or support ventilation [63].
- 3) [Lorazepam](#) is less likely than [diazepam](#) to produce significant [respiratory depression](#), particularly in children who have received other anticonvulsants (especially [phenobarbital](#)). If [respiratory depression](#) is going to occur, it generally develops after the first dose, or not at all [37].

### 3.3.16] Other

#### 3.3.16.A] Drug abuse

- 1) Use of benzodiazepines, including [lorazepam](#), may lead to physical and psychological dependence. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patient with significant personality disorders. Patients who are addiction-prone should be closely monitored while receiving [lorazepam](#). Withdrawal symptoms can appear following discontinuation of recommended [lorazepam](#) doses after as little as one week of therapy [3].
- 2) Unless the patient already has an alcohol or drug abuse problem, survey studies and clinical data have found that benzodiazepine-treated patients rarely become regular users or abusers of their prescribed medication. According to System to Retrieve Information from Drug Evidence (STRIDE) data compiled by the DEA, [diazepam](#) has the highest rate of illicit use with all other benzodiazepines having only negligible rates of abuse in comparison. [Alprazolam](#) and [lorazepam](#) were found to be more [diazepam](#)-like than [oxazepam](#), [halazepam](#), or [chlordiazepoxide](#) by some investigators. Frequency of abuse, however, not only depends upon reinforcing/subjective/behavioral effects of the particular benzodiazepine, but upon local customs and fads, drug availability, and knowledge of the drug's actions [90].

#### 3.3.16.B] Drug withdrawal

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

#### 3.3.16.C] Somnolence

See Drug Consult reference: ANTIHISTAMINE IMPAIRMENT OF DRIVING

#### 3.3.16.D] Withdrawal sign or symptom

- 1) Use of benzodiazepines, including [lorazepam](#), may lead to physical and psychological dependence. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patient with significant personality disorders. Patients who are addiction-prone should be closely monitored while receiving [lorazepam](#). Withdrawal symptoms can appear following discontinuation of recommended [lorazepam](#) doses after as little as one week of therapy [3].
- 2) Abrupt withdrawal of [lorazepam](#) may precipitate withdrawal seizures. The exact cause of the seizures is unknown, but it is proposed that the rapid decline of serum levels and lack of long-acting metabolites are major factors. Experience dictates that patients should be slowly tapered off [lorazepam](#) [91].

- 3j) Probable lorazepam withdrawal occurred in a 51-year-old female who had a 2-month history of lorazepam use (exact pattern unknown). The patient exhibited nausea (unresponsive to prochlorperazine), agitation, insomnia, fatigue, and nervousness. Lorazepam blood level 18 hours post admission was 31 ng/mL. Forty eight hours post admission, the patient became disoriented, rigid, catatonic, and had a staggering gait [92].
- 4j) Tinnitus has been reported associated with drug withdrawal [89].
- 5j) Grand-mal type seizures have been reported secondary to abrupt lorazepam withdrawal [93] [91].
- 6j) The long-term daily use of benzodiazepines (at least 3 months) in therapeutic doses is associated with a mild, but significant withdrawal syndrome after discontinuation [89]. Withdrawal symptoms were different than those of anxiety, and included involuntary movements, paresthesias, perceptual changes, confusion and persistent tinnitus. Withdrawal symptoms reportedly occurred sooner in patients who had been receiving the shorter-acting benzodiazepines as compared to those receiving longer-acting agents; symptoms resolved after a period of 4 weeks. These data suggest that gradual reduction in the dose of benzodiazepines is indicated for achieving abstinence in outpatients.
- 7j) Mania occurred in an 83-year-old woman following the abrupt withdrawal of benzodiazepines [94]. Five years previously, the patient was prescribed diazepam 2 mg orally 3 times daily which was taken for approximately 2 years; at that time, lorazepam (1 mg 3 times daily) was substituted for diazepam and was taken for approximately 3 years. The patient discontinued lorazepam abruptly approximately 4 weeks prior to presentation. The patient improved with thioridazine. However, the patient was treated 2 months later for a severe depressive illness and subsequently developed a further manic episode, similar to the first episode. It is unclear if the first manic episode was the result of lorazepam withdrawal.

### 3.4j Teratogenicity/Effects in Pregnancy/Breastfeeding

#### Aj) Teratogenicity/Effects in Pregnancy

##### 1j) U.S. Food and Drug Administration's Pregnancy Category: Category D (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

##### 2j) 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

##### 3j) Crosses Placenta: Yes

##### 4j) Clinical Management

a) Lorazepam crosses the placenta and may cause fetal damage when administered during pregnancy. Manufacturers recommend use during pregnancy only during serious or life threatening emergencies where safer drugs cannot be used or are ineffective. Possibility of potential pregnancy must be considered at time of administration. Advise patients to discontinue use if they become pregnant. There are insufficient data on administration during cesarean section; therefore, use is not recommended [3] [12] [2]. All benzodiazepines can be expected to cross the placenta. Teratogenicity with lorazepam has not been confirmed; however, other benzodiazepines have demonstrated



teratogenic potential [238]. Thus, use of [lorazepam](#) 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 [239]. In contrast to benzodiazepines, the non-benzodiazepines [zolpidem](#) and [zaleplon](#) are in Pregnancy Risk Categories B and C, respectively [240] [241].

## 5) Literature Reports

**a)** A single case has recently been reported of [aplasia cutis congenita](#) in a neonate born to a mother who had used [lorazepam](#) and [diazepam](#) or [chlordiazepoxide](#) in the early part of her pregnancy; however, a direct causal relationship could not be clearly established nor other causes ruled out [226].

**b)** High dose IV [lorazepam](#) therapy has been shown to cause "floppy infant" syndrome [227] [228]. Fifty-three neonates born to 51 mothers treated with [lorazepam](#) were followed for 5 days. Maternal plasma levels were higher than corresponding cord levels. Cord levels greater than 45 mcg/L necessitated ventilation at birth in 40 infants (75%). Conjugated [lorazepam](#) was measurable for up to 7 days following birth. Preterm neonates had a high incidence of low Apgar scores, need for ventilation, hypothermia, and poor suckling. Full term neonates whose mothers received oral [lorazepam](#) showed no complications other than delay in feeding [228]. [Lorazepam](#) use during labor has been associated with an increased, while not statistically significant, occurrence of [respiratory depression](#) in the newborn [229]. In animal studies using 10 times the maximum human dose, [lorazepam](#) was associated with decreased weight and increased activity in offspring [230]. Withdrawal symptoms lasting several days have occurred in neonates born to women receiving benzodiazepines prior to delivery [231] [232].

**c)** Placental transfer has been indicated in blood levels obtained from umbilical cords in humans. Infants whose mothers ingested benzodiazepines for several weeks or more prior to delivery, reportedly experienced withdrawal symptoms during the postnatal period. Neonates whose mothers ingested benzodiazepines during the late phase of pregnancy or at delivery, experienced symptoms such as hypoactivity, hypotonia, hypothermia, [respiratory depression](#), [apnea](#), trouble feeding and impaired metabolic response to cold stress [3] [12] [2].

**d)** 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 [233].

e) The controversy over prescribing benzodiazepines during pregnancy is discussed in an extensive review [234]. Both animal data and human epidemiological studies suggest benzodiazepines are teratogens. Attack on the CNS by benzodiazepines can occur during organogenesis, during early differentiation of neural anlagen (hereditary factor) after neural tube closing, or during biochemical differentiation of the brain. However, other researchers have presented letters citing their own data which show benzodiazepines to be free of teratogenic potential [235], [236] [237].

## **B) Breastfeeding**

1) American Academy of Pediatrics Rating: Drugs for which the effect on nursing infants is unknown but may be of concern.

2) World Health Organization Rating: Compatible with breastfeeding.

3) Micromedex Lactation Rating: Infant risk is minimal.

a) The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding.

## **4) Clinical Management**

a) According to the World Health Organization, benzodiazepines given in single doses or for a short duration to breastfeeding mothers probably does not pose a risk to the breastfeeding infant [243]. However, the American Academy of Pediatrics considers [lorazepam](#) to have effects on the nursing infant that are unknown, but of possible concern [242]. Manufacturers do not recommend administration to breastfeeding women unless maternal benefit outweighs the infant risk. Sedation and inability to suckle have occurred in nursing infants whose mother's have ingested benzodiazepines. Monitoring and observation of nursing infants for pharmacological effects are highly recommended [3] [12] [2]. The available literature has shown that [lorazepam](#) administration to lactating mothers appears to pose minimal risk to the infants [245] [246] [247] [248] [249]. However, because newborns and premature infants have diminished glucuronidation capabilities, [lorazepam](#) could theoretically accumulate resulting in sedation; such infants should be observed for lethargy or feeding problems. The risk to the nursing infant appears to depend on the specific benzodiazepine agent used, and the risks of other benzodiazepine therapy among lactating women cannot be ruled out. This risk should be minimized by using drugs that have established safety records at the lowest dosage for the shortest possible duration [249].

## **5) Literature Reports**

a) [Lorazepam](#) is distributed into breast milk in low concentrations, and the amount ingested by the nursing infant is pharmacologically insignificant [244]. Conjugation and elimination of [lorazepam](#) are slow in the infant [245]. A slight delay in establishing breastfeeding between infant and mother has resulted from the presence of [lorazepam](#) in breast milk [246]. However, the volume of milk consumed and the duration of nursing sessions were not significantly affected by maternal ingestion of [lorazepam](#) [247]. One report suggested that [lorazepam](#) is safe for oral premedication in breastfeeding mothers, since the concentration found in breast milk was low (8 to 9 ng/mL) [248]. In one case, a neonate did not show signs of sedation after the breastfeeding mother took 2.5 mg [lorazepam](#) twice daily for five days after delivery [244]. The results of the aforementioned studies and

other studies were reviewed, and the authors concluded that no adverse effects have been reported with the use of lorazepam during lactation [249].

#### 6) Drug Levels in Breastmilk

##### a) Parent Drug

##### 1) Milk to Maternal Plasma Ratio

a) 0.22 [248]

### 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 [120]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [121]. 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 [122].

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 [119].

##### 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 [136] [137] [138] [139] [140].

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 [127] [128] [129] [130] [131].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.C] Anileridine

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.D] Aprobarbital

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

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].

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 [127] [128] [129] [130] [131].

**b))** Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.E] [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 [125].
- 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 [125].
- 7)) Probable Mechanism: additive [respiratory depression](#)

### 3.5.1.F] [Butabarbital](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

**b))** Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

**3.5.1.G] Butalbital**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

**3.5.1.H] 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 [167] [168]. 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 [167] [168]. 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.I] Carisoprodol**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].
- 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.J] [Chloral Hydrate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: [Chloral](#) hydrate, with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [197]. 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.K] [Chlorzoxazone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].
- 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] [Clozapine](#)

- 1) Interaction Effect: CNS depression
- 2) Summary: Two cases have been reported in which concomitant use of [clozapine](#) and [lorazepam](#) resulted in marked sedation, [excessive salivation](#), and ataxia [123]. The manufacturer advises caution when giving [clozapine](#) with a benzodiazepine [124].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for signs of intoxication (eg, marked sedation, dizziness, ataxia, weakness, decreased cognition or motor performance, [excessive salivation](#)). If symptoms are present, reduce [lorazepam](#) dose.
- 7) Probable Mechanism: additive

#### 3.5.1.M] [Codeine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.N] [Dantrolene](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].

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.O] [Desogestrel](#)

1) Interaction Effect: decreased [lorazepam](#) effectiveness

2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.

7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)

8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].



c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.P] Dienogest

- 1) Interaction Effect: decreased [lorazepam](#) effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.Q] 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 [201]. 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](#) [201]. 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 (C<sub>max</sub>) of [diazepam](#) could be calculated, as the plasma concentration of [diazepam](#) was undetectable at all sample time points except for 2 hours. After dong quai, [diazepam](#) C<sub>max</sub> 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 [200].

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 [200].

### 3.5.1.RJ [Drospirenone](#)

1J) Interaction Effect: decreased [lorazepam](#) effectiveness

2J) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.

7J) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)

8J) Literature Reports

aJ) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

bJ) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while

receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.S] Estradiol Cypionate

- 1) Interaction Effect: decreased lorazepam effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam [192] [193] [194]. Women taking combination contraceptives may require a higher dose of lorazepam [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of lorazepam
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.T] Estradiol Valerate

- 1) Interaction Effect: decreased lorazepam effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam [192] [193] [194]. Women taking combination contraceptives may require a higher dose of lorazepam [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable

- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of lorazepam
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

#### 3.5.1.U] Ethchlorvynol

- 1) Interaction Effect: additive respiratory depression
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [206].
- 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.V] Ethinyl Estradiol

- 1) Interaction Effect: decreased lorazepam effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam [192] [193] [194]. Women taking combination contraceptives may require a higher dose of lorazepam [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of lorazepam
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [187] [188]. In seven healthy women

receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

**b)** The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

**c)** Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.W] [Ethinodiol Diacetate](#)

**1)** Interaction Effect: decreased [lorazepam](#) effectiveness

**2)** Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].

**3)** Severity: minor

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.

**7)** Probable Mechanism: increased hepatic metabolism of [lorazepam](#)

**8)** Literature Reports

**a)** Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

**b)** The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

**c)** Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.X] [Etonogestrel](#)

**1)** Interaction Effect: decreased [lorazepam](#) effectiveness

- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.Y] [Fentanyl](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death [196]. 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](#) [122]. 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 [196].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents [196].
- 7) Probable Mechanism: additive CNS depression

### 3.5.1.Z] [Flumazenil](#)

- 1) Interaction Effect: precipitation of seizures
- 2) Summary: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [112].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [112].
- 7) Probable Mechanism: abrupt discontinuation of the anticonvulsant protective effect

#### 3.5.1.AA] Fospropofol

- 1) Interaction Effect: additive cardiorespiratory effects
- 2) Summary: Concomitant use of fospropofol and a benzodiazepine may result in additive cardiorespiratory effects due to the sedative action of both drugs [96]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) 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.
- 7) Probable Mechanism: CNS depression

#### 3.5.1.AB] [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 [214].
- 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 [214].
- 7) Probable Mechanism: additive CNS depression

#### 3.5.1.AC] [Hydromorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines



are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.AD] 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](#) [155]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [156].

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 [154].

### 3.5.1.AE] [Levonorgestrel](#)

1) Interaction Effect: decreased [lorazepam](#) effectiveness

2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.

7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)

**8) Literature Reports**

- a)** Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].
- b)** The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].
- c)** Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

**3.5.1.AF] [Levorphanol](#)**

- 1)** Interaction Effect: additive [respiratory depression](#)
- 2)** Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].
- 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 [119].

**3.5.1.AG] [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 [198] and use with caution [199].
- 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 [198] and use with caution [199].
- 7) Probable Mechanism: additive CNS depression

### 3.5.1.AH] Magnolia

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [162] [163] [164]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [165]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [166]. 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 [157].

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 +/- 6.78 minutes after a 5 mg/kg loading dose, and 56.24 +/- 7.30 minutes after a 10 mg/kg loading dose. The bioavailability as expressed as area under the curve (AUC) was 58.87 +/- 4.19 micrograms/milliliter/minute (mcg/mL/minute) after a 5 mg/kg loading dose, and 133.89 +/- 16.26 mcg/mL/minute ( $p$  less than 0.05) after a 10 mg/kg loading dose [158].

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 [159].

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) [160].

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 [161].

### 3.5.1.AI] [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](#) [181] [182] [183] 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](#) [181] [182] [183] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.
- 7) Probable Mechanism: additive effects

### 3.5.1.AJ] [Medroxyprogesterone Acetate](#)

- 1) Interaction Effect: decreased [lorazepam](#) effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.AK] [Meperidine](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.AL] [Mephensin](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].

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.AM] Mephobarbital**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

**3.5.1.AN] Meprobamate**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].
- 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.AO] Mestranol**

- 1) Interaction Effect: decreased [lorazepam](#) effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)

## 8) Literature Reports

- a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].
- b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].
- c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.AP] [Metaxalone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].
- 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.AQ] [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 [118].
- 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 [118].
- 7) Probable Mechanism: additive CNS depression effects

**3.5.1.AR] Methocarbamol**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [207] [208] [209] [210].
- 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.AS] Methohexital**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

**3.5.1.AT] 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 [126].
- 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 [126].



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 [126].

### 3.5.1.AU] [Morphine](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

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

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.AW] [Norelgestromin](#)

1) Interaction Effect: decreased [lorazepam](#) effectiveness



- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous [lorazepam](#) 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of [lorazepam](#) (and [oxazepam](#)) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

#### 3.5.1.AX] [Norethindrone](#)

- 1) Interaction Effect: decreased [lorazepam](#) effectiveness
- 2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of [lorazepam](#) [192] [193] [194]. Women taking combination contraceptives may require a higher dose of [lorazepam](#) [195].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [lorazepam](#) therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of [lorazepam](#)
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of [lorazepam](#), which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing [norethindrone](#) 1 mg and [ethinyl estradiol](#) 50 mcg for at least six months, the administration of intravenous [lorazepam](#) 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of [lorazepam](#). The total clearance of [lorazepam](#) was increased 3.7-fold as compared with that of eight healthy control females [189].

**b)** The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

**c)** Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.AY] Norgestimate

**1)** Interaction Effect: decreased lorazepam effectiveness

**2)** Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam [192] [193] [194]. Women taking combination contraceptives may require a higher dose of lorazepam [195].

**3)** Severity: minor

**4)** Onset: delayed

**5)** Substantiation: probable

**6)** Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.

**7)** Probable Mechanism: increased hepatic metabolism of lorazepam

**8)** Literature Reports

**a)** Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [189].

**b)** The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

**c)** Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

### 3.5.1.AZ] Norgestrel

**1)** Interaction Effect: decreased lorazepam effectiveness

**2)** Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam [192] [193] [194]. Women taking combination contraceptives may require a higher dose of lorazepam [195].

**3)** Severity: minor

**4)** Onset: delayed

- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
- 7) Probable Mechanism: increased hepatic metabolism of lorazepam
- 8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [187] [188]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [189].

b) The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [190].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [191]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

#### 3.5.1.BA] Olanzapine

- 1) Interaction Effect: potentiation of excessive sedation and cardiorespiratory depression
- 2) Summary: The concomitant use of intramuscularly administered olanzapine and parenteral benzodiazepines (diazepam, lorazepam, midazolam) is not recommended due to the potentiation of excessive sedation and cardiorespiratory depression [172].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of intramuscularly administered olanzapine and parenteral benzodiazepines (diazepam, lorazepam, midazolam) is not recommended due to additive CNS depression [172].
- 7) Probable Mechanism: additive CNS depression

#### 3.5.1.BB] 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 [95].
- 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 [95].
- 7) Probable Mechanism: unknown

**3.5.1.BC] 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 [178] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [179].
- 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 [178] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [179].
- 7) Probable Mechanism: additive effects

**3.5.1.BD] Oxymorphone**

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].
- 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 [119].

**3.5.1.BE] 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 [144]. 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 [144]. 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 [144].

**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 [173]. 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 [174]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [175].

**3.5.1.BF] Pentobarbital**

**1) Interaction Effect:** additive respiratory depression

**2) Summary:** When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].

**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 [127] [128] [129] [130] [131].

**b))** Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.BG] 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 [211].
- 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 [211].
- 7)) Probable Mechanism: additive CNS depression

### 3.5.1.BH] Phenobarbital

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

**b))** Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows



intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.BI] [Posaconazole](#)

- 1) Interaction Effect: decreased [posaconazole](#) serum concentration
- 2) Summary: The concomitant use of [posaconazole](#) and [lorazepam](#) appears to decrease [posaconazole](#) concentrations, especially with higher [posaconazole](#) doses (eg, 800 mg/day). Based on a small retrospective study (n=18), coadministration of [posaconazole](#) (primarily metabolized by uridine diphosphate glucuronosyltransferase (UGT) [213]) with [lorazepam](#) (a possible inducer of UGT), resulted in significantly lower [posaconazole](#) levels compared with no concurrent benzodiazepine. Avoid coadministration of [posaconazole](#) with [lorazepam](#). [Temazepam](#) may be a reasonable alternative to [lorazepam](#) during [posaconazole](#) therapy [212].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Avoid concomitant use of [posaconazole](#) and [lorazepam](#), especially in patients with low [posaconazole](#) levels. If appropriate, [temazepam](#) may be a reasonable alternative to [lorazepam](#) during [posaconazole](#) therapy [212].
- 7) Probable Mechanism: induction of uridine diphosphate glucuronosyltransferase (UGT)-mediated metabolism of [posaconazole](#) by [lorazepam](#)
- 8) Literature Reports

a) In a retrospective review of hospitalized adults receiving [posaconazole](#), steady-state trough [posaconazole](#) concentrations were significantly reduced when coadministered with [lorazepam](#). Routine therapeutic drug monitoring of [posaconazole](#) was preformed on 560 serum samples from 195 patients, including 31 samples from 18 patients taking concomitant [lorazepam](#). Concurrent use of [lorazepam](#) was defined as any intake within 3 days before obtaining the [posaconazole](#) level. Mean [posaconazole](#) levels were lower with [lorazepam](#) coadministration (438 nanograms (ng)/mL; median, 336 ng/mL) compared with no concurrent benzodiazepine (744 ng/mL; median, 585 ng/mL; p=0.001). When [posaconazole](#) dose was evaluated, median [posaconazole](#) levels were significantly lower with concomitant [lorazepam](#) with [posaconazole](#) 800 mg/day (292 ng/mL; p=0.002) but not with [posaconazole](#) 600 mg/day (512 ng/mL; p=0.186) when compared with no concurrent benzodiazepine (585 ng/mL). [Temazepam](#) coadministration with [posaconazole](#) did not result in significantly lower [posaconazole](#) levels (53 samples in 27 patients). Investigators postulated that [lorazepam](#) induces [posaconazole](#) clearance by glucuronidation [212].

### 3.5.1.BJ] [Primidone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.BK] [Probenecid](#)

1)) Interaction Effect: [lorazepam](#) toxicity

2)) Summary: In a randomized study, the use of oral [probenecid](#) 500 mg every six hours and intravenous [lorazepam](#) 2 mg in nine healthy volunteers resulted in a 45% decrease in [lorazepam](#) total clearance. The half-life increased by 130% (from 14 to 33 hours) [141]. When [probenecid](#) and [lorazepam](#) are coadministered, the dose of [lorazepam](#) should be reduced by 50% [142].

3)) Severity: moderate

4)) Onset: delayed

5)) Substantiation: probable

6)) Clinical Management: The dose of [lorazepam](#) should be reduced by 50% when coadministered with [probenecid](#). Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance).

7)) Probable Mechanism: decreased [lorazepam](#) metabolism

### 3.5.1.BL] [Propoxyphene](#)

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.BM] [Pyrimethamine](#)

- 1) Interaction Effect: elevated liver function tests
- 2) Summary: Mild [hepatotoxicity](#) has been reported in some patients when [lorazepam](#) and [pyrimethamine](#) are administered concomitantly [185] [186]. It is not known if concurrent use of [pyrimethamine](#) with other benzodiazepines would cause the same effect.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If [lorazepam](#) and [pyrimethamine](#) are to be given concomitantly, monitor liver function regularly. Avoid giving this combination to patients with known [hepatic dysfunction](#).
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) Two of five healthy adult women experienced [hepatotoxicity](#) (elevations in [bilirubin](#) and serum transaminases) when [lorazepam](#) and [pyrimethamine](#) were coadministered. Neither patient had alterations in liver function tests when each agent was given alone. No adverse hepatic effects were noted in the other three patients during combined [lorazepam](#) and [pyrimethamine](#) therapy [184]. To date, there are no reports on the use of [pyrimethamine](#) with other benzodiazepines.

### 3.5.1.BN] [Remifentanyl](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [121]. 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](#) [122].
- 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 [119].

### 3.5.1.BO] [Secobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.BP] 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 [204] [205]. 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 (IC<sub>50</sub>) 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 IC<sub>50</sub> of [diazepam](#) was 0.029 mcM [202].

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](#) [203].

### 3.5.1.BQ] Sodium Oxybate

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [97]. 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.BR] 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 [113] [114] [115] [116]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [113]. 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 [113] [114] [115] [116]. Because benzodiazepines are metabolized by CYP3A4 pathways, similar results would be expected if any benzodiazepine was coadministered with St. John's wort. Therefore, consider monitoring for alterations in the therapeutic and adverse effects of the benzodiazepine if used concomitantly with St. John's wort. If a patient is taking St. John's wort at the time of surgery during which [midazolam](#) or any other benzodiazepine is to be used for sedation, consider monitoring the patient closely for signs of reduced benzodiazepine effectiveness and adjusting the benzodiazepine dose, if necessary.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism of the benzodiazepine by St. John's wort
- 8) Literature Reports

a) Concomitant use of [quazepam](#) and St. John's wort decreased [quazepam](#) plasma concentrations, but did not affect [quazepam](#) efficacy, in a randomized, double-blind, placebo-controlled, crossover study of 13 healthy adult males. Participants refrained from grapefruit-containing products and herbal supplements or tea; caffeine-containing products were withheld. Participants received either oral St. John's wort (standardized to 0.3% hypericin) 300 mg 3 times/day or placebo for 14 days. On day 14, a single [quazepam](#) 15-mg oral dose was given. Blood samples were obtained just prior to and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hrs after the [quazepam](#) dose. At 48 hrs, [quazepam](#) C<sub>max</sub> 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<sub>max</sub> and t(1/2) and 2-oxoquazepam C<sub>max</sub>, AUC, T<sub>max</sub>, and t(1/2) were not significantly affected by St. John's wort. The 2-oxoquazepam to [quazepam](#) ratio in the C<sub>max</sub> 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 [113].

**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) [114].

**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 [117].

**d)** St. John's wort reduced the bioavailability of oral midazolam by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous midazolam 0.05 mg/kg. Oral midazolam syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same midazolam doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and Cmax of oral midazolam were reduced by 50%, and oral clearance increased 2-fold (all  $p$  less than 0.05). AUC of intravenous midazolam was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of midazolam with reduced availability likely due to CYP3A4 induction at the gut wall [115].

**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) [116].

### 3.5.1.BS] Sufentanil

**1)** Interaction Effect: additive respiratory depression

**2)** Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [120]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [121]. 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](#) [122].

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 [119].

### 3.5.1.BT] 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 [143].

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 [143].

7) Probable Mechanism: additive CNS depression

### 3.5.1.BU] Tan-Shen

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

2) Summary: Miltirone and the other nine diterpene quinones present in *Salvia miltiorrhiza* (Tan-shen) appear to act as partial agonists at central benzodiazepine receptors [177]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [177]. Because tan-shen acts as a partial and not a full agonist, the clinical significance of the interaction is unknown. Caution is advised until the magnitude of the interaction is better understood.

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

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

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



**8) Literature Reports**

**a)** Ten diterpene quinones present in the Chinese medicinal herb *Salvia miltiorrhiza* (tan-shen) have been shown to inhibit binding of (3H) flunitrazepam to central benzodiazepine receptors. These quinones, isolated from the ethereal extract of the roots of *Salvia miltiorrhiza*, exhibited IC50s ranging from 0.3 to 36.2 mcml (the IC50 is the drug concentration required to provide 50% inhibition of specific (3H) flunitrazepam binding). Miltirone had the highest potency (IC50=0.3 mcml) [176]. 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](#) [176].

**3.5.1.BV] Tapentadol**

- 1)** Interaction Effect: an increase in central nervous system and [respiratory depression](#)
- 2)** Summary: The concomitant use of tapentadol with central nervous system depressants including sedatives (eg, [alprazolam](#), [midazolam](#), or [zolpidem](#)) may result in additive CNS and respiratory depressant effects, including hypotension, profound sedation and/or coma. When administering tapentadol and a sedative together, dosage of one or both agents may be reduced [180].
- 3)** Severity: major
- 4)** Onset: unspecified
- 5)** Substantiation: theoretical
- 6)** Clinical Management: Consider monitoring the patient for cardiorespiratory depression when tapentadol and sedatives are used in combination. A reduction in dose of one or both drugs may be necessary [180].
- 7)** Probable Mechanism: additive effects

**3.5.1.BW] Teduglutide**

- 1)** Interaction Effect: increased exposure of orally administered benzodiazepines
- 2)** Summary: Coadministration of teduglutide with an oral medication that requires titration, such as a benzodiazepine, may significantly increase absorption of the benzodiazepine. In clinical trials, a patient taking a benzodiazepine who was treated with concomitant teduglutide experienced altered mental status that progressed to coma. A reduced dose of oral drugs requiring titration (eg, benzodiazepines) may be necessary when administered concomitantly with teduglutide [153]. 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 [153]. 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 [153].

### 3.5.1.BX] Theophylline

- 1) Interaction Effect: decreased benzodiazepine effectiveness
- 2) Summary: Theophylline has been shown to reverse the sedative effects of benzodiazepines [107] [108] [109] [110]. 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 [111].
- 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 [98].

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 [99]. Other studies and case reports have also shown that theophylline antagonizes the sedative effects of diazepam [100] [101].

c) Three case reports described patients who had the sedative effects of lorazepam reversed postoperatively by the administration of aminophylline 1 mg/kg intravenously [102]. This same aminophylline dose was used to reverse the sedative effects of midazolam in three other patients [103]. Theophylline also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [104].

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 [105].

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 [106].

### 3.5.1.BY] [Thiopental](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [136] [137] [138] [139] [140].
- 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 [127] [128] [129] [130] [131].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [132]. 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 [133]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [134]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [135].

### 3.5.1.BZ] [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 [144]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [152] [145]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [145]. 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 [144]. 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 resulted in additive CNS depressive effects or may decreased the effectiveness of benzodiazepines. It is recommended that patients

be asked about herbal product use during intake of personal history [144] [145]. Monitor for altered effectiveness of the benzodiazepine during concurrent use.

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

**8j) 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 [144].

**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 [146] [147]. Valeriana officinalis extracts significantly displaced fluorodiazepam from benzodiazepine receptors, and a fraction containing sesquiterpene alcohols and ketones showed 80% inhibition at concentrations of  $1.5 \times 10^{-3}$  moles/liter. A fraction containing valepotriates also produced significant displacement. Statistical values were not provided [148]. 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 [149]. 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 [150].

**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 IC<sub>50</sub> values. IC<sub>50</sub> values for the hydroalcoholic extract were 0.04 milligrams/milliliter (mg/ml) and  $3.9 \times 10^{-3}$  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* [151].

### 3.5.1.CA] Valproic Acid

- 1) Interaction Effect: increased lorazepam concentrations
- 2) Summary: In a small study of healthy subjects (n=8), valproic acid was found to decrease lorazepam clearance by 40% compared to controls [170]. When lorazepam and valproic acid are coadministered, the dose of lorazepam should be reduced by 50% [171].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: When lorazepam and valproic acid are coadministered, the dose of lorazepam should be reduced by 50%. The patient should then still be monitored for evidence of lorazepam toxicity, including excessive sedation and respiratory depression.
- 7) Probable Mechanism: decreased lorazepam metabolism
- 8) Literature Reports

a) In a study involving six healthy male subjects, the coadministration of intravenous lorazepam 2 mg with oral valproic acid 250 twice daily for three days resulted in a decrease of 40% in the total clearance of lorazepam. The lorazepam-glucuronide formation rate was also decreased by 55%. Plasma concentrations of lorazepam were approximately two times higher for at least 12 hours following concurrent administration. The manufacturer of lorazepam recommends reducing the dose of lorazepam by 50% during valproic acid coadministration [169].

### 3.5.1.CB] 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 [215].
- 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 [215].
- 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 lorazepam
- 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 [221] [222] [223].

- 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 [220].

### 3.5.2.B) Ethanol

- 1) Interaction Effect: increased sedation
- 2) Summary: Ethanol enhances the adverse psychomotor effects and decreases the ability to do tasks requiring alertness when used with [lorazepam](#). Acutely, ethanol may inhibit benzodiazepine metabolism, especially in patients with borderline liver disease [217] [218] [219].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients receiving [lorazepam](#) should be advised against ethanol use.
- 7) Probable Mechanism: additive CNS depression
- 8) Literature Reports

a) Short-term administration of ethanol 0.8 g/kg, followed by 0.5 g/kg PO every 5 hours for 4 doses, reduced intravenous [lorazepam](#) clearance by 18%, but did not significantly alter the half-life [216]. The significance of these findings is unclear.

## 3.5.5] Intravenous Admixtures

### 3.5.5.1] Drugs

#### 3.5.5.1.A] [Acetaminophen](#)

- 1) Compatible

a) [Acetaminophen](#) with [lorazepam](#) in a 50:50 admixed ratio was physically and chemically compatible for up to 4 hours at room temperature using Y-site methodology in a one-way compatibility test (stability of [acetaminophen](#) only was tested). The manufacturer does not recommend that any drug be admixed, infused simultaneously through the same IV line, or added to an infusion device containing [acetaminophen](#) [524].

**3.5.5.1.B] Acyclovir****1) Compatible**

- a) **Acyclovir** 5 mg/mL in **Dextrose** 5% in water with **lorazepam** 40 mcg/mL in **Dextrose** 5% in water visually compatible for 24 hours at 25 degrees C under fluorescent light [538].

**3.5.5.1.C] Allopurinol Sodium****1) Compatible**

- a) **Allopurinol** sodium 3 mg/mL in **Sodium chloride** 0.9% injection with **lorazepam** 0.1 mg/mL in **Sodium chloride** 0.9% injection, compatible for up to 4 hours at 22 degrees C [497]

**3.5.5.1.D] Amifostine****1) Compatible**

- a) **Amifostine** 10 mg/mL in **Dextrose** 5% in water with **lorazepam** 0.1 mg/mL in 5% **Dextrose** injection, compatible during simulated Y-site administration [532]

**3.5.5.1.E] Amsacrine****1) Compatible**

- a) **Amsacrine** 1 mg/mL with **lorazepam** 0.1 mg/mL visually compatible in **Dextrose** 5% in water for a 4-hour study period at room temperature under fluorescent lighting [553]

**3.5.5.1.F] Atracurium****1) Compatible**

- a) **Atracurium** (500 mcg/mL with **lorazepam** 500 mcg/mL visually compatible for 24 hours at 28 degrees C in **Dextrose** 5% in water under fluorescent light) [503]
- b) **Lorazepam** (500 mcg/mL with **atracurium** 500 mcg/mL visually compatible for 24 hours at 28 degrees C in **Dextrose** 5% in water under fluorescent light) [504]

**3.5.5.1.G] Atropine****1) Compatible**

- a) **Atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL and **lorazepam** 2 or 4 mg/1 mL, visually and chemically compatible for 48 hours at 25 degrees C in syringe [500]
- b) **Lorazepam** (2 or 4 mg/1 mL with **meperidine** 50 or 100 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe; **lorazepam** 2 or 4 mg/1 mL and **atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe) [501]
- c) **Meperidine** (**meperidine** 50 or 100 mg/1 mL and **atropine** 0.4 mL of a 1 mg/mL solution with **lorazepam** 2 or 4 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe) [521]



- d) **Lorazepam** 2 or 4 mg/mL with 0.53 mL or 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL, visually compatible for 24 hours at 25 degrees C or less [533]
- e) **Lorazepam** 2 or 4 mg/mL with 1 mL of **morphine** 8 or 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 24 hours at 25 degrees C or less [533]
- f) **Lorazepam** 2 mg/mL with 1 mL of **morphine** 8 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of **Dextrose** 5% in water [533]
- g) **Lorazepam** 4 mg/mL with 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of Lactated Ringer's or Ringer's injection [533]
- h) **Lorazepam** 2 mg/mL with 0.53 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of **Sodium chloride** 0.9% [533]
- i) **Lorazepam** 2 or 4 mg/mL with 0.53 mL of **morphine** 8 mg/mL or 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL, visually compatible for 48 hours at 25 degrees C [533]
- j) **Atropine** 0.4 mL of a 1 mg/mL solution with **lorazepam** 2 or 4 mg/1 mL, visually and chemically compatible for 48 hours at 25 degrees C in syringe [535]
- k) **Atropine** 0.4 mL of a 1 mg/mL solution and **morphine** 0.53 mL of an 8 mg/mL or 1 mL of a 15 mg/mL solution with **lorazepam** 2 or 4 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in syringe [535]
- l) **Atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL and **lorazepam** 2 or 4 mg/1 mL, visually and chemically compatible for 48 hours at 25 degrees C in syringe [535]

#### 3.5.5.1.H] **Aztreonam**

##### 1) Incompatible

- a) **Aztreonam** 40 mg/mL in 5% **Dextrose** in water with **lorazepam** 0.1 mg/mL in **Dextrose** 5% in water, haze and turbidity greater than 0.1 NTU formed within 1 hour; observed with high-density light enhancement, not visible in normal fluorescent room light [554]

#### 3.5.5.1.I] **Buprenorphine**

##### 1) Incompatible

- a) **Buprenorphine** with **lorazepam** in a 1:1 volume ratio incompatible at room temperature [530]

#### 3.5.5.1.J] **Butorphanol**

##### 1) Compatible



a) **Butorphanol** 1 or 2 mg/mL with **lorazepam** 2 or 4 mg/mL, physically compatible for 24 hours at 25 degrees C in direct admixture in syringe or when added to any of the solutions listed below [552]:

Dextrose 5% in water

Lactated Ringer's injection

Ringer's injection

Sodium chloride 0.9%

#### **3.5.5.1.K] Caspofungin Acetate**

##### **1) Compatible**

a) **Caspofungin** acetate 0.7 mg/mL diluted in 0.9% **sodium chloride** injection with **lorazepam** 0.5 mg/mL is physically compatible for 4 hours at room temperature (approximately 23 degrees C) during simulated Y-site administration [502].

#### **3.5.5.1.L] Ceftaroline Fosamil**

##### **1) Compatible**

a) **Lorazepam** 0.5 mg/mL and ceftaroline fosamil 2.22 mg/mL (diluted with either 0.9% **sodium chloride**, 5% **dextrose**, or lactated Ringer injection) were compatible for at least 4 hours at room temperature (23 degrees C) under fluorescent light during simulated Y-site administration [522].

#### **3.5.5.1.M] Cimetidine**

##### **1) Compatible**

a) **Cimetidine** 300 mg/2 mL with **lorazepam** 2 mg/1 mL visually compatible in direct admixture in syringe for 4 hours at 25 degrees C [526]

#### **3.5.5.1.N] Dexamethasone**

##### **1) Compatible**

a) **Dexamethasone** 4 mg/1 mL with **lorazepam** 0.5 mL of a 2 mg/mL solution, physically compatible for 2 hours in direct admixture in syringe; temperature not specified [546]

#### **3.5.5.1.O] Dexamethasone Sodium Phosphate**

##### **1) Conflicting Data**

##### **a) Incompatible**

1) The stability and compatibility of 40 mg of **dexamethasone sodium phosphate**, 200 mg of **diphenhydramine** hydrochloride, 4 mg of **lorazepam**, and 400 mg of **metoclopramide** hydrochloride solutions diluted to 100 mL with 0.9% **sodium chloride** were studied in a portable infusion pump. **Dexamethasone**,

diphenhydramine, and metoclopramide were stable over 14 days at 30 degrees Celsius (near-body temperature). However, lorazepam steadily decreased over time and by the 14th day, only 31% of the initial concentration was remaining. Furthermore, even at 24 hours, slightly more than 85% of the initial concentration was remaining. Thus, author concluded that the combination of dexamethasone, diphenhydramine, lorazepam, and metoclopramide in the concentration studied should not be administered [499].

2) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in dextrose 5% in water, concentration of lorazepam dropped below 90% between 3 and 4 hours after admixing when stored in polyvinylchloride bags at room temperature under fluorescent light; however, the same 3-drug admixture in dextrose 5% in water was chemically stable for up to 24 hours when admixed in glass bottles [506].

3) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in sodium chloride 0.9% injection, concentration of lorazepam dropped below 90% between 4 and 8 hours after admixing when stored in polyvinylchloride bags at room temperature under fluorescent light; however, the same 3-drug admixture in sodium chloride 0.9% injection was chemically stable for up to 24 hours when admixed in glass bottles [507].

4) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in sodium chloride 0.9% injection, is not recommended. Solutions containing lorazepam compounded in sodium chloride 0.9% had a higher particle content than corresponding solutions compounded in dextrose 5% [508].

#### b) Compatible

1) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in dextrose 5% in water, was chemically stable for up to 24 hours when stored in glass bottles at room temperature under fluorescent light; however, when this 3-drug combination was stored in polyvinylchloride containers, the concentration of lorazepam dropped below 90% between 3 and 4 hours after admixing [514].

2) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in dextrose 5% in water was chemically stable for up to 24 hours when stored in glass bottles at room temperature under fluorescent light; however, when this 3-drug combination was stored in polyvinylchloride containers, the concentration of lorazepam dropped below 90% between 3 and 4 hours after admixing [515].

3) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in sodium chloride 0.9% injection, is not recommended. Solutions containing lorazepam compounded in sodium chloride 0.9% had a higher particle content than corresponding solutions compounded in dextrose 5% [510].

**3.5.5.1.P] Diphenhydramine****1) Compatible**

a) **Diphenhydramine** (50 mg/1 mL with **lorazepam** 0.5 mL of a 2 mg/mL solution physically compatible for 2 hours in direct admixture in syringe; temperature not specified) [521]

b) **Lorazepam** (1 mg/0.5 mL with **diphenhydramine** 50 mg/1 mL physically compatible for 2 hours; conditions not specified) (Tech Info **Opticrom**(R), 1988)

**3.5.5.1.Q] Diphenhydramine Hydrochloride****1) Incompatible**

a) The stability and compatibility of 40 mg of **dexamethasone sodium phosphate**, 200 mg of **diphenhydramine** hydrochloride, 4 mg of **lorazepam**, and 400 mg of **metoclopramide** hydrochloride solutions diluted to 100 mL with 0.9% **sodium chloride** were studied in a portable infusion pump. **Dexamethasone**, **diphenhydramine**, and **metoclopramide** were stable over 14 days at 30 degrees Celsius (near-body temperature). However, **lorazepam** steadily decreased over time and by the 14th day, only 31% of the initial concentration was remaining. Furthermore, even at 24 hours, slightly more than 85% of the initial concentration was remaining. Thus, author concluded that the combination of **dexamethasone**, **diphenhydramine**, **lorazepam**, and **metoclopramide** in the concentration studied should not be administered [499].

**3.5.5.1.R] Doripenem****1) Compatible**

a) Doripenem 5 mg/mL with **lorazepam** 0.5 mg/mL in either 5% **dextrose** injection or in 0.9% **sodium chloride** injection is physically compatible for 4 hours at room temperature (approximately 23 degrees C) under fluorescent light during simulated Y-site administration [531].

**3.5.5.1.S] Fenoldopam Mesylate****1) Compatible**

a) **Fenoldopam** mesylate 80 mcg/mL in **Sodium chloride** 0.9% injection with **lorazepam** 0.5 mg/mL in **Sodium chloride** 0.9% injection, visually and physically compatible for up to 4 hours at 23 degrees C in a clear glass tube under constant fluorescent light during simulated Y-site administration [544].

**3.5.5.1.T] Fentanyl****1) Compatible**

a) **Fentanyl** (1, 1.5, or 2 mL of a 0.05 mg/mL solutions with **lorazepam** 0.5 mL of a 4 mg/mL solution visually compatible for 24 hours at 25 degrees C in direct admixture in syringe) [521]

b) **Lorazepam** (2 mg/0.5 mL with **fentanyl** 50 mcg/1 mL, 75 mcg/1.5 mL or 100 mcg/2 mL visually compatible for 24 hours at 25 degrees C or less in syringe; with **fentanyl** visually

compatible for 3 hours in syringe at 25 degrees C and then added to a running, 125 mL/hr, infusion; solutions and drug concentrations listed below) [545]:

lorazepam 2 mg/1 mL with fentanyl 50 mcg/1 mL in Lactated Ringer's injection

lorazepam 4 mg/1 mL with fentanyl 75 mcg/1.5 mL in Ringer's injection

lorazepam 4 mg/1 mL with fentanyl 100 mcg/2 mL in Sodium chloride 0.9%

#### 3.5.5.1.U] Filgrastim

##### 1) Compatible

a) Filgrastim 30 mcg/mL in Dextrose 5% in water with lorazepam 0.1 mg/mL in Dextrose 5% in water, compatible for up to 4 hours at 22 degrees C [529]

#### 3.5.5.1.V] Fludarabine

##### 1) Compatible

a) Fludarabine 1 mg/mL with lorazepam 0.1 mg/mL, both in Dextrose 5% in water, visually compatible for a 4-hour study period at room temperature under fluorescent light [541]

#### 3.5.5.1.W] Foscarnet

##### 1) Conflicting Data

###### a) Incompatible

1) Foscarnet 24 mg/mL with lorazepam 4 mg/mL, gas production reported [540]

###### b) Compatible

1) Foscarnet 24 mg/mL with lorazepam 0.08 mg/mL visually compatible, macroscopically and microscopically, in Dextrose 5% in water or Sodium chloride 0.9% for 24 hours at 25 degrees C under fluorescent light [542]

2) Foscarnet 24 mg/mL with lorazepam 4 mg/mL, gas production reported [543]

#### 3.5.5.1.X] Fosphenytoin

##### 1) Compatible

a) Fosphenytoin and lorazepam were stable at a Y-site over an 8-hour period [555]. Medication preparation included a 5-milliliter (mL) aliquot made from a 50-milligram (mg)/mL fosphenytoin 10-mL intravenous (IV) vial diluted to 50 mL with 0.9% sodium chloride injection. To this aliquot, 5 mL of lorazepam 2-mg/mL IV injection was added and maintained at ambient temperature.

#### 3.5.5.1.Y] Gallium Nitrate

##### 1) Incompatible

a) **Gallium nitrate (Ganite(R))** 1 mg/mL admixed from a plastic syringe in a 1:1 ratio simulating Y-site administration with **lorazepam** 1 mg/mL, both in **Sodium chloride** 0.9%, white haze with precipitation that cleared after 30 minutes and remained clear for 24-hour study period, stored at room temperature under fluorescent light in a glass container; chemical stability not tested [539]

#### 3.5.5.1.Z] **Glycopyrrolate**

##### 1) Compatible

a) **Lorazepam** 2 or 4 mg/1 mL with 1.5 mL of a **glycopyrrolate** 200 mcg/mL solution, visually and chemically compatible for 48 hours at 25 degrees C in syringe [512]

#### 3.5.5.1.AA] **Granisetron Hydrochloride**

##### 1) Compatible

a) **Granisetron** hydrochloride 1 mg/mL in 0.9% **Sodium chloride** with **lorazepam** 4 mg in 40 mL of 0.9% **Sodium chloride** in PVC bag (protected from light), stable for 4 hours when mixed in 1:1 ratio during simulated Y-site administration [537]

b) **Granisetron** hydrochloride diluted with 5% **dextrose** injection to a concentration of 50 mcg/mL is compatible with **lorazepam** at a concentration of 0.1 mg/mL (D5W) during simulated Y-site injection. Compatibility was measured using visual examinations in fluorescent light and in high-intensity monodirectional light. Turbidity, particle size and particle counts were completed for certain solutions. The mixtures were assessed at 1 and 4 hours (Trissel, 1997).

#### 3.5.5.1.AB] **Haloperidol**

##### 1) Compatible

a) **Haloperidol** 5 mg/1 mL with **lorazepam** 2 or 4 mg/1 mL, physically compatible for 4 hours in syringe; temperature not specified [517]

b) **Haloperidol** in a 1:1 mixture with **lorazepam**, physically compatible for 16 hours at room temperature; drug concentrations not specified [518]

#### 3.5.5.1.AC] **Idarubicin**

##### 1) Incompatible

a) **Idarubicin** 1 mg/mL in **Sodium chloride** 0.9% with **lorazepam** 2 mg/mL, undiluted, immediate moderate color change reported which persisted throughout a 24-hour study period at 25 degrees C under fluorescent light [536]

#### 3.5.5.1.AD] **Linezolid**

##### 1) Compatible

a) **Linezolid** 2 mg/mL (tested undiluted) with **lorazepam** 0.1 mg/mL (diluted in 5% **dextrose** injection) is physically compatible for 4 hours at room temperature (approximately 23 degrees C) under fluorescent light during simulated Y-site administration [498].

**3.5.5.1.AE] Meperidine****1) Compatible**

- a) **Atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL and **lorazepam** 2 or 4 mg/1 mL, visually and chemically compatible for 48 hours at 25 degrees C in syringe [500]
- b) **Lorazepam** (2 or 4 mg/1 mL with **meperidine** 50 or 100 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe; **lorazepam** 2 or 4 mg/1 mL and **atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe) [501]
- c) **Meperidine** (**meperidine** 50 or 100 mg/1 mL and **atropine** 0.4 mL of a 1 mg/mL solution with **lorazepam** 2 or 4 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe) [521]
- d) **Meperidine** (50 or 100 mg/1 mL with **lorazepam** 2 or 4 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in direct admixture in syringe) [521]
- e) **Atropine** 0.4 mL of a 1 mg/mL solution with **meperidine** 50 or 100 mg/1 mL and **lorazepam** 2 or 4 mg/1 mL, visually and chemically compatible for 48 hours at 25 degrees C in syringe [535]

**3.5.5.1.AF] Metoclopramide Hydrochloride****1) Incompatible**

- a) The stability and compatibility of 40 mg of **dexamethasone sodium phosphate**, 200 mg of **diphenhydramine** hydrochloride, 4 mg of **lorazepam**, and 400 mg of **metoclopramide** hydrochloride solutions diluted to 100 mL with 0.9% **sodium chloride** were studied in a portable infusion pump. **Dexamethasone**, **diphenhydramine**, and **metoclopramide** were stable over 14 days at 30 degrees Celsius (near-body temperature). However, **lorazepam** steadily decreased over time and by the 14th day, only 31% of the initial concentration was remaining. Furthermore, even at 24 hours, slightly more than 85% of the initial concentration was remaining. Thus, author concluded that the combination of **dexamethasone**, **diphenhydramine**, **lorazepam**, and **metoclopramide** in the concentration studied should not be administered [499].

**3.5.5.1.AG] Micafungin Sodium****1) Compatible**

- a) **Lorazepam** 0.5 mg/mL with **micafungin** sodium 1.5 mg/mL (both diluted in 0.9% **sodium chloride** injection) is physically compatible for 4 hours at room temperature, approximately 23 degrees C, under fluorescent light during simulated Y-site administration [523].

**3.5.5.1.AH] Milrinone Lactate****1) Compatible**

- a) **Lorazepam** 0.2 mg/mL with **milrinone** lactate 400 mcg/mL in **Dextrose** 5% injection, stable for 4 hours at 22 to 23 degrees C in glass containers or polyvinyl **chloride** bags under fluorescent light during simulated Y-site administration [549].
- b) **Lorazepam** 1 mg/mL with **milrinone** lactate 200 mcg/mL (4 mLs of each) in **Dextrose** 5% injection, physically compatible for 4 hours at 25.6 degrees C in a glass vial under well-lighted conditions during simulated Y-site administration [550].
- c) **Lorazepam** 2 mg/mL with **milrinone** lactate 200 mcg/mL (4 mLs of each) in **Dextrose** 5% injection, physically compatible for 4 hours at 25.6 degrees C in a glass vial under well-lighted conditions during simulated Y-site administration [550].

### 3.5.5.1.A1] **Morphine**

#### 1) Compatible

- a) **Lorazepam** 2 or 4 mg/mL with 0.53 mL or 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL, visually compatible for 24 hours at 25 degrees C or less [533]
- b) **Lorazepam** 2 or 4 mg/mL with 1 mL of **morphine** 8 or 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 24 hours at 25 degrees C or less [533]
- c) **Lorazepam** 2 mg/mL with 1 mL of **morphine** 8 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of **Dextrose** 5% in water [533]
- d) **Lorazepam** 4 mg/mL with 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of Lactated Ringer's or Ringer's injection [533]
- e) **Lorazepam** 2 mg/mL with 0.53 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL solution, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of **Sodium chloride** 0.9% [533]
- f) **Lorazepam** 2 or 4 mg/mL with 0.53 mL of **morphine** 8 mg/mL or 1 mL of **morphine** 15 mg/mL and 0.4 mL of **atropine** 1 mg/mL, visually compatible for 48 hours at 25 degrees C [533]
- g) **Lorazepam** 2 or 4 mg/mL with 0.53 mL or 1 mL of **morphine** 15 mg/mL, visually compatible for 24 hours at 25 degrees C or less [533]
- h) **Lorazepam** 2 or 4 mg/mL with 1 mL of **morphine** 8 or 15 mg/mL solution, visually compatible for 24 hours at 25 degrees C or less [533]
- i) **Lorazepam** 2 mg/mL with 1 mL of **morphine** 8 mg/mL, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of Lactated Ringer's injection [533]
- j) **Lorazepam** 4 mg/mL with 1 mL of **morphine** 15 mg/mL, visually compatible for 3 hours at 25 degrees C and then added to a running, 125 mL/hr, infusion of Ringer's injection [533]
- k) **Lorazepam** 2 or 4 mg/mL with 0.53 mL or 1 mL of **morphine** 15 mg/mL, visually compatible for 48 hours at 25 degrees C [533]



1) **Atropine** 0.4 mL of a 1 mg/mL solution and **morphine** 0.53 mL of an 8 mg/mL or 1 mL of a 15 mg/mL solution with **lorazepam** 2 or 4 mg/1 mL visually and chemically compatible for 48 hours at 25 degrees C in syringe [535]

#### 3.5.5.1.AJ] **Nalbuphine**

##### 1) Compatible

a) **Lorazepam** 2 or 4 mg/1 mL with **nalbuphine** 10 mg/1 mL, visually compatible in syringe for 24 hours at 25 degrees C [551]

#### 3.5.5.1.AK] **Ondansetron**

##### 1) Conflicting Data

###### a) Incompatible

1) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water with **ondansetron** 1 mg/mL in **Sodium chloride** 0.9% results in the formation of a very light haze [511] [508].

###### b) Compatible

1) .

2) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water with **ondansetron** 1 mg/mL in **Sodium chloride** 0.9% resulted in the formation of a very light haze [509] [510]

#### 3.5.5.1.AL] **Ondansetron Hydrochloride**

##### 1) Conflicting Data

###### a) Incompatible

1) **Dexamethasone sodium phosphate** 20 mg/mL with **lorazepam** 2 mg/mL and **ondansetron** hydrochloride 32 mg/mL, all admixed in **dextrose** 5% in water, concentration of **lorazepam** dropped below 90% between 3 and 4 hours after admixing when stored in polyvinylchloride bags at room temperature under fluorescent light; however, the same 3-drug admixture in **dextrose** 5% in water was chemically stable for up to 24 hours when admixed in glass bottles [506].

2) **Dexamethasone sodium phosphate** 20 mg/mL with **lorazepam** 2 mg/mL and **ondansetron** hydrochloride 32 mg/mL, all admixed in **sodium chloride** 0.9% injection, concentration of **lorazepam** dropped below 90% between 4 and 8 hours after admixing when stored in polyvinylchloride bags at room temperature under fluorescent light; however, the same 3-drug admixture in **sodium chloride** 0.9% injection was chemically stable for up to 24 hours when admixed in glass bottles [507].

3) **Dexamethasone sodium phosphate** 20 mg/mL with **lorazepam** 2 mg/mL and **ondansetron** hydrochloride 32 mg/mL, all admixed in **sodium chloride** 0.9% injection, is not recommended. Solutions containing **lorazepam** compounded in

sodium chloride 0.9% had a higher particle content than corresponding solutions compounded in dextrose 5% [508].

**b) Compatible**

1) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in dextrose 5% in water, was chemically stable for up to 24 hours when stored in glass bottles at room temperature under fluorescent light; however, when this 3-drug combination was stored in polyvinylchloride containers, the concentration of lorazepam dropped below 90% between 3 and 4 hours after admixing [514].

2) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in dextrose 5% in water was chemically stable for up to 24 hours when stored in glass bottles at room temperature under fluorescent light; however, when this 3-drug combination was stored in polyvinylchloride containers, the concentration of lorazepam dropped below 90% between 3 and 4 hours after admixing [515].

3) Dexamethasone sodium phosphate 20 mg/mL with lorazepam 2 mg/mL and ondansetron hydrochloride 32 mg/mL, all admixed in sodium chloride 0.9% injection, is not recommended. Solutions containing lorazepam compounded in sodium chloride 0.9% had a higher particle content than corresponding solutions compounded in dextrose 5% [510].

**3.5.5.1.AM] Paclitaxel**

**1) Compatible**

a) Lorazepam 0.1 mg/mL in Dextrose 5% injection with paclitaxel 1.2 mg/mL in Dextrose 5% injection in glass container, no visual or turbidimetric evidence of incompatibility in simulated Y-site injection for a 4-hour study period, admixture stored at room temperature under fluorescent light [505]. However, this admixture was not tested for chemical stability.

**3.5.5.1.AN] Pancuronium**

**1) Compatible**

a) Lorazepam 0.5 mg/mL with pancuronium 0.05 mg/mL, visually compatible for 24 hours at 28 degrees C in Dextrose 5% in water under fluorescent light [516]

**3.5.5.1.AO] Piperacillin Sodium/Tazobactam Sodium**

**1) Compatible**

a) Piperacillin sodium 40 mg/mL plus tazobactam 5 mg/mL in Dextrose 5% in water with lorazepam 0.1 mg/mL in Dextrose 5% in water, compatible for 4 hours at 22 degrees C [534]

**3.5.5.1.AP] Propofol**

**1) Compatible**

a) **Propofol** 1% injectable emulsion and **lorazepam** 0.1 milligram/milliliter in a 1:1 volume mixture (simulated Y-site administration) are visually compatible in polycarbonate test tubes at 15 minutes and 1 hour at approximately 23 degrees Celsius as determined by visualization with fluorescent light and a high-intensity, mono-directional light source (Tyndall beam) [547].

#### 3.5.5.1.AQ] **Ranitidine**

##### 1) Conflicting Data

###### a) Incompatible

1) **Lorazepam** 4 mg/1 mL with **ranitidine** 50 mg/2 mL, physically compatible in syringe for 1 hour at 25 degrees C under fluorescent light; however, physical compatibility is questionable due to the viscosity of **lorazepam** which causes poor mixing and layering which disappeared following vortex mixing [519]

###### b) Compatible

1) **Lorazepam** 4 mg/1 mL with **ranitidine** 50 mg/2 mL, physically compatible in syringe for 1 hour at 25 degrees C under fluorescent light; however, physical compatibility is questionable due to the viscosity of **lorazepam** which causes poor mixing and layering which disappeared following vortex mixing [520]

#### 3.5.5.1.AR] **Sargramostim**

##### 1) Incompatible

a) **Lorazepam** 0.1 mg/mL with **sargramostim** 10 mcg/mL, both in **sodium chloride** 0.9%, formation of a slightly bluish, hazy solution reported within 1 hour at 22 degrees C under fluorescent light [548]

#### 3.5.5.1.AS] **Tacrolimus**

##### 1) Compatible

a) **Lorazepam** 1 mg/mL in 5% **Dextrose** injection with **tacrolimus** 1 mg/mL in 0.9% **Sodium chloride** injection, visually compatible for 24 hours at room temperature under fluorescent light [513]

#### 3.5.5.1.AT] **Vecuronium**

##### 1) Compatible

a) **Lorazepam** 0.5 mg/mL with vecuronium 0.1 mg/mL, visually compatible for 24 hours at 28 degrees C in **Dextrose** 5% in water under fluorescent light [527]

#### 3.5.5.1.AU] **Vinorelbine**

##### 1) Compatible

- a) Lorazepam 0.1 mg/mL in Sodium chloride 0.9% with vinorelbine 1 mg/mL in Sodium chloride 0.9%, compatible for up to 4 hours at 22 degrees C [528]

#### 3.5.5.1.AV] Zidovudine

##### 1) Compatible

- a) Lorazepam 80 mg/L with zidovudine 4 g/L both in Dextrose 5% in water, visually compatible, macroscopically and microscopically, for a 4-hour study period at 25 degrees C under fluorescent light in a polyolefin container [525]

#### 3.5.5.2] Solutions

##### 3.5.5.2.A] DEXTROSE 5%

##### 1) Compatible

a) In a letter to the editor, one institution reported that on several occasions they noted a precipitate of lorazepam during infusions by volumetric pump. They administer lorazepam with dextrose 5% at a concentration of 0.1 or 0.2 milligrams/milliliter in an evacuated glass container. This is used for prolonged sedation of adult intensive care patients and delivered by a volumetric infusion pump with a vented, polyethylene-lined administration set, administered into a central vein. Precipitation appears less frequently when the temperature is greater than 25 degrees Celsius. They hypothesize that this may be the combined result of a low drug solubility and agitation by the volumetric pump [556].

b) In a letter to the editor, precipitation of lorazepam was noted almost immediately when admixtures were made with the 4 milligram per milliliter vials (mg/mL) but NO precipitation was noted when admixtures were prepared with the 2 mg/mL vials. Admixtures contained 40 milligrams (mg) of lorazepam diluted in either 5% dextrose injection or 0.9% sodium chloride injection to yield a final concentration of 1 mg/mL. To minimize the risk of precipitation, lorazepam admixtures are now prepared from the 2 mg/mL vials only (Levanda M, 1998). Lorazepam admixtures with concentrations of 1 milligram per milliliter (mg/mL) and 2 mg/mL in 5% DEXTROSE injection were shown to be stable when stored for 28 hours at room temperature (22 degrees Celsius) in a GLASS BOTTLE following preparation with the 2 mg/mL and 4 mg/mL lorazepam preparations, respectively. A 0.16 mg/mL solution prepared from the 4 mg/mL lorazepam preparation in a 5% DEXTROSE injection and stored in a GLASS BOTTLE at room temperature under fluorescent room light remained stable at 28 hours following preparation. Lorazepam 1 mg/mL prepared from the 2 mg/mL preparation in 5% DEXTROSE injection, stored in POLYPROPYLENE SYRINGES for 28 hours at room temperature was found to be stable. During the 28 hour observation period, all solutions retained more than 90% of their initial lorazepam concentration [557].

##### 3.5.5.2.B] DEXTROSE 5% in water

##### 1) Compatible

- a) Dextrose 5% in water with lorazepam 4 mg/L, stable for up to 24 hours at 25 degrees C in glass, polyvinylchloride or polyolefin containers [558] [559]

b) **Dextrose** 5% in water with **lorazepam** 400 or 800 mg/L at 25 degrees C, stable for 24 hours in a glass container, stable for 7 hours in a Viaflex(R) polyvinylchloride container and stable for 4 hours in a Lifecare(R) polyvinylchloride container [558] [559]

### 3.5.5.2.C] LACTATED RINGER'S INJECTION

#### 1) Compatible

a) Lactated Ringer's injection (when **lorazepam** 2 mg/mL in **Dextrose** 5% in water or 1 mg/mL in **Sodium chloride** 0.9% or Sterile water for injection was injected into a running, 125 mL/hr, infusion the effluent was found to be clear and colorless) [521]

### 3.5.5.2.D] RINGER'S INJECTION

#### 1) Compatible

a) Ringer's injection (when **lorazepam** 2 mg/mL in **Sodium chloride** 0.9% or Sterile water for injection or 1 mg/mL in **Dextrose** 5% in water was injected into a running, 125 mL/hr, infusion the effluent was found to be clear and colorless) [521]

### 3.5.5.2.E] SODIUM CHLORIDE 0.9%

#### 1) Compatible

a) **Lorazepam** 4 mg/L in **Sodium chloride** 0.9%, stable for up to 24 hours at 25 degrees C in glass, polyvinylchloride or polyolefin containers [560] [561]

b) **Lorazepam** 400 or 800 mg/L in **Sodium chloride** 0.9% at 25 degrees C, stable for 24 hours in a glass container, stable for 7 hours in a Viaflex(R) polyvinylchloride container and stable for 4 hours in a Lifecare(R) polyvinylchloride container [560] [561]

c) In a letter to the editor, precipitation of **lorazepam** was noted during a continuous infusion to an agitated, critically ill patient requiring mechanical ventilation. The infusion contained **lorazepam** 150 milligrams in 300 milliliters of **sodium chloride** 0.9% (0.5 milligrams/milliliter(mg/mL)). To minimize the risk of precipitation, they now prepare **lorazepam** infusion from the 2 mg/mL multidose vials with **dextrose** 5% at a concentration of 0.5 mg/mL in a glass container at room temperature [562].

d) In a letter to the editor, precipitation of **lorazepam** was noted almost immediately when admixtures were made with the 4 milligram per milliliter vials (mg/mL) but NO precipitation was noted when admixtures were prepared with the 2 mg/mL vials. Admixtures contained 40 milligrams (mg) of **lorazepam** diluted in either 5% **dextrose** injection or 0.9% **sodium chloride** injection to yield a final concentration of 1 mg/mL. To minimize the risk of precipitation, **lorazepam** admixtures are now prepared from the 2 mg/mL vials only (Levanda M, 1998).

e) **Lorazepam** 1 mg/mL prepared from the 2 mg/mL preparation in 0.9% **SODIUM CHLORIDE** stored in POLYPROPYLENE SYRINGES for 28 hours at room temperature was found to be stable. During the 28 hour observation period, all solutions retained more than 90% of their initial **lorazepam** concentration [563].

### 3.5.5.2.F] Total Parenteral Nutrition

#### 1) Compatible

a) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water added to total parenteral nutrition solution compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below [564]:

Amino acids 10% (Aminosyn(R) II)	
Dextrose	5
Sterile water for injection	516.8 mL
Potassium phosphates	3.5 mEq
Sodium chloride	25 mEq
Potassium chloride	35 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.3 mEq

b) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water added to total parenteral nutrition solution compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below [564]:

Amino acids 10% (FreAmine(R) III)	
Dextrose	5
Sterile water for injection	516.75 mL
Sodium chloride	37.5 mEq
Potassium chloride	40 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	5 mEq

c) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water added to total parenteral nutrition solution compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below [564]:

Amino acids 10% (Aminosyn(R) II)	4
Dextrose	25%
Sterile water for injection	161 mL
Potassium phosphates	1 mEq
Sodium chloride	25 mEq
Potassium chloride	18 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	9.15 mEq

d) **Lorazepam** 0.1 mg/mL in **Dextrose** 5% in water added to total parenteral nutrition solution compatible in simulated Y-site administration for 4 hours at 23 degrees C; specific composition of total parenteral nutrition solution listed below [564]:

Amino acids 10% (FreAmine(R) III)	4
Dextrose	25%

Sterile water for injection	158.6 mL
Potassium phosphates	5.75 mEq
Sodium chloride	40 mEq
Potassium chloride	25 mEq
Magnesium sulfate	8 mEq
Multivitamins	10 mL
Trace elements	1 mL
Calcium gluconate	7.5 mEq

## 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) Therapeutic

##### 1) Anxiety

- a) Decreased anxiety and associated symptoms may indicate efficacy.
- b) Assess periodically for therapeutic usefulness with long-term use [2].

##### 2) Status Epilepticus

- a) Cessation of seizure indicates efficacy.

##### 3) Preanesthetic

- a) Diminished recall, decreased anxiety, and sedation may indicate efficacy.

#### B) Toxic

##### 1) Laboratory Parameters

###### a) Oral

- 1) Monitor blood counts periodically in patients on long-term therapy [2].
- 2) Monitor liver function tests periodically in patients on long-term therapy [2].

##### 2) Physical Findings

###### a) Oral

- 1) Monitor elderly or debilitated patients frequently for sedation [2].



2j) Monitor for symptoms of upper gastrointestinal disease frequently in geriatric patients and patients on long-term therapy [2].

**b)) Injection**

1j) In patients treated for status epilepticus, monitor vital signs while on parenteral therapy. If respiratory depression occurs, monitor respiration status closely [12].

## 4.2] Patient Instructions

### Aj) Lorazepam (By mouth)

#### Lorazepam

Treats anxiety.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an [allergic reaction](#) to [lorazepam](#) or similar medicines, or if you have acute [narrow-angle glaucoma](#).

How to Use This Medicine:

Tablet, Liquid

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

Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

Mix the oral solution with water, juice, soda, applesauce, or pudding. Drink or eat the mixture right away.

Do not store it for later use.

Missed dose: Take a dose as soon as you remember. If you are more than 1 hour late, skip the missed dose and wait until it is time for your next dose. Do not use extra medicine to make up for a missed dose.

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

Oral solution: Refrigerate the oral solution. Throw away an opened bottle after 90 days.

Drugs and Foods to Avoid:

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

Some medicines can affect how [lorazepam](#) works. Tell your doctor if you are also using any of the following:

[Theophylline](#), [aminophylline](#)

[Clozapine](#)

[Probenecid](#)

[Valproate](#)

Medicine to treat seizures

Medicine to treat depression or mental illness

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:

Tell your doctor if you are pregnant or breastfeeding, or if you have [glaucoma](#), liver disease, lung problems, or a history of depression, alcohol or drug addiction, or seizures.

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 drowsy. Do not drive or do anything else that could be dangerous until you know how this medicine affects you.

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

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

**Possible Side Effects While Using This Medicine:**

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

Depression, confusion, thoughts of hurting yourself

Severe drowsiness or weakness, slow heartbeat, trouble breathing

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

Dizziness, clumsiness

Unusual tiredness

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

**B) Lorazepam (Injection)**

**Lorazepam**

Treats seizure disorders, such as [epilepsy](#). Also used before certain medical procedures, such as surgery, to relieve anxiety. Belongs to a class of drugs called benzodiazepines.

**When This Medicine Should Not Be Used:**

You should not receive this medicine if you have had an [allergic reaction to lorazepam](#), if you are pregnant, or if you have [narrow-angle glaucoma](#), severe lung disease, or [sleep apnea](#) (temporary stopping of breathing during sleep).

**How to Use This Medicine:**

**Injectable**

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given through a needle placed in one of your veins or given as a shot into one of your muscles.

A nurse or other health provider will give you this medicine.

**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 using [clozapine \(Clozaril®\)](#), [haloperidol \(Haldol®\)](#), [loxapine \(Loxitane®\)](#), [probenecid \(Benemid®\)](#), [phenobarbital](#), [scopolamine](#), or [valproate \(Depakene®\)](#).

Tell your doctor if you are using [birth control pills](#), an MAO inhibitor (such as [Eldepryl®](#), [Marplan®](#), [Nardil®](#), [Parnate®](#)), or a phenothiazine medicine (such as [prochlorperazine](#), [Compazine®](#), [Mellaril®](#), [Phenergan®](#), [Thorazine®](#), [Trilafon®](#)).

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

Do not drink alcohol while you are using this medicine.

**Warnings While Using This Medicine:**

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

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

If you develop any unusual or strange thoughts and behavior while taking [lorazepam](#) injection, be sure to discuss it with your doctor. Some changes that have occurred in people taking this medicine are like those seen in people who drink too much alcohol. Other changes might be confusion, agitation, and hallucinations (seeing, hearing, or feeling things that are not there).

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.

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  
 Blue lips, fingernails, or skin.  
 Fever, chills, **cough**, sore throat, and body aches.  
 Increase in how much or how often you urinate.  
 Lightheadedness or fainting.  
 Loss of consciousness.  
 Pain, itching, burning, swelling, or a lump under your skin where the needle is placed.  
 Painful or difficult urination.  
 Problems with vision, speech, or walking.  
 Seizures.  
 Severe muscle weakness or trouble standing.  
 Shortness of breath.  
 Slurred speech, confusion, or severe drowsiness.  
 Trouble concentrating or memory loss.

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

Dry mouth, headache, tiredness, nausea and vomiting.  
 Irritability or agitation.

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

#### 4.3] Place In Therapy

**A) LORAZEPAM** is an effective anxiolytic and hypnotic agent for the treatment of anxiety and insomnia. **Lorazepam** has a shorter elimination half-life than **diazepam**, with metabolism to inactive metabolites. Therefore, aging and liver or **renal diseases** have little effect on **lorazepam** disposition.

**B) Lorazepam** is indicated for the treatment of **status epilepticus**. **Lorazepam** may be preferred over **diazepam**, as the former agent possesses a higher affinity to the binding receptor on **GABA**, a longer duration of action, more potent on a milligram to milligram basis [284] [285] [286], and is less likely to produce significant **respiratory depression** [37]. However, **lorazepam** may be less effective in patients who are chronically receiving benzodiazepine anticonvulsants and in those who will need the drug more than once [287].

**C) Lorazepam** is equally effective as **diazepam** as a **preanesthetic medication**; the amnestic effects of **lorazepam** are slightly delayed in comparison to those of **diazepam**.

**D) If administered in small doses, lorazepam** may be preferred over other benzodiazepines in patients with severely impaired liver function, as the formation of glucuronides is not restricted to the hepatic endoplasmic reticulum [24]. See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUSEA AND VOMITING

#### 4.4] Mechanism of Action / Pharmacology

##### A) MECHANISM OF ACTION

**1) Lorazepam** is a benzodiazepine derivative in clinical use as a sedative-hypnotic, anticonvulsant, anxiolytic, and muscle relaxant. **Lorazepam** binds to the **GABA(A)** receptor in the central nervous system and facilitates the action of **GABA (gamma-aminobutyric acid)**, an inhibitory neurotransmitter. **GABA** augments the binding of benzodiazepines by increasing their affinity of the receptor for the drug and

benzodiazepines modulate **GABA** binding. The **GABA** receptor is a complex structure with several subunit binding sites for benzodiazepines, picrotoxin, and **GABA**. These binding sites control the frequency of opening an associated **chloride** channel. Benzodiazepines enhance the inhibitory effect of **GABA** on neuronal excitability by increasing neuronal membrane permeability to **chloride**, thereby leading to membrane hyperpolarization, which is believed to mediate the sedative/hypnotic/anticonvulsant/muscle relaxant properties of the benzodiazepines [275] [276].

2) There also appears to be a direct peripheral action on the contractile process of muscle. Enhancement of **GABA** activity in the limbic area and mesencephalic reticular formation is responsible for anticonvulsant properties. Benzodiazepines prevent the spread of seizures without affecting the spike activity of the primary focus [277].

3) On the EEG (**electroencephalogram**), benzodiazepines reduce alpha activity and an elevation in low-voltage fast activity, especially beta activity. Tolerance occurs to these effects. Benzodiazepines also reduce sleep latency, reduces the number of awakenings and the time spent in stage 0 (stage of wakefulness). The time spent in stage 1 (descending drowsiness) is usually reduced, but is variable. Benzodiazepines increase the amount of time spent in stage 2 (which is the major fraction of non-rapid eye movement (REM) sleep) and reduces the amount of time in stage 3 and 4 (slow-wave sleep). The reduction in stage 4 is associated with a decrease in night terrors and nightmares. The time spent in REM sleep is reduced; however, the number of cycles of REM sleep is increased. Therefore, an increase in total sleep time is noted, along with a sense of a deep and refreshing sleep [263].

4) Animal data indicates that **lorazepam** alters either the registration phase of the memory process or events occurring immediately thereafter [278]. **Impairment of psychomotor** function occurs with doses greater than or equal to 1 mg and persist for up to 12 hours. Morning-hangover effects are prevalent after hypnotic use of **lorazepam** [279].

#### 4.5] Therapeutic Uses

##### 4.5.A] Agitation - **Psychotic disorder**

###### 1) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

###### 2) Summary:

The combination of **haloperidol** and **lorazepam** was suggested to be more effective than **lorazepam** alone in agitated patients presenting to the psychiatric emergency service [39].

Repeated doses of either **lorazepam** 2 mg or **haloperidol** 5 mg were equally effective for the early treatment of acute agitation in psychotic patients in a double-blind, randomized study (n=98) [40]

###### 3) Adult:

a) The combination of **haloperidol** and **lorazepam** was suggested to be more effective than **lorazepam** alone in agitated patients presenting to the psychiatric emergency service. Patients who met clinical criteria for the use of chemical restraints and had a minimum score of 4 on the Overt Aggression Scale

received either [lorazepam](#) 2 mg (n=11) or [haloperidol](#) 5 mg and [lorazepam](#) 2 mg (n=9). Combination therapy was significantly better than [lorazepam](#) alone after 1 hour according to the Overt Aggression Scale and the visual analog scale (p less than 0.05). However, on the Clinical Global Impressions severity scale, the comparison was not significant. With repeated measures of analyses of variance, both groups improved over time [39].

b)) Repeated doses of either [lorazepam](#) 2 mg or [haloperidol](#) 5 mg were equally effective for the early treatment of acute agitation in psychotic patients. In a double-blind, randomized study, 98 patients received either intramuscular [lorazepam](#), [haloperidol](#), or both. Patients received 1 to 6 injections in a 12 hour period depending upon clinical need. Effective symptom reduction was achieved in each treatment group with significant decreases from baseline at every hourly evaluation (p less than 0.01). Mean differences on the Agitated Behavior Scale and modified Brief Psychiatric Rating Scale suggested that tranquilization was most rapid in patients receiving the combination therapy (p less than 0.05) [40].

#### 4.5.B) [Alcohol withdrawal syndrome](#)

##### 1)) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

##### 2)) Summary:

Benzodiazepines are considered the drugs of choice for treatment of acute ethanol withdrawal [1]

All are effective [1]

#### 4.5.C) [Anxiety](#)

FDA Labeled Indication

##### 1)) Overview

FDA Approval: Adult, yes; Pediatric, [yes \(oral only; 12 years and older\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

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

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

##### 2)) Summary:

[Lorazepam](#) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms [2] [3].

Anxiety or tension as a result of the stress of everyday life usually does not require treatment with [lorazepam](#) [3] [2].

Effectiveness for more than 4 months has not been assessed by systematic clinical studies [3] [2].

In a double-blinded, randomized, placebo-controlled trial (n=276), pregabalin and [lorazepam](#) were more effective than placebo in the treatment of [generalized anxiety disorder](#) [4].

### 3) Adult:

a) [Lorazepam](#) is an effective anxiolytic [5] [6] [7] [8]. Effective doses for anxiolytic effects have been 1 to 2 mg (up to 6 mg) orally twice to three times daily.

b) In a manufacturer-sponsored, double-blinded, randomized, placebo-controlled trial, pregabalin and [lorazepam](#) were more effective than placebo in the treatment of [generalized anxiety disorder](#). Patients (n=276) were randomized to 1 of 4 treatment arms: pregabalin 150 mg/day, pregabalin 600 mg/day, [lorazepam](#) 6 mg/day, or placebo. The study consisted of a 1-week placebo lead-in phase, a 4-week treatment phase and a 1-week taper. Each treatment arm showed a decrease in the total Hamilton Anxiety Scale (HAM-A) score from baseline. However, the decrease was significantly greater in the pregabalin 150 mg/day (p=0.03), pregabalin 600 mg/day (p=0.003) and [lorazepam](#) arms (0.0001) compared with placebo. Pregabalin 600 mg/day and [lorazepam](#) also showed a significant decrease in the HAM-A psychic subscale compared with placebo (p=0.008, p=0.001). Pregabalin 150 mg/day showed a decrease but this decrease did not reach statistical significance (p=0.09). Dizziness (30.9%) was the most frequently reported adverse effect associated with pregabalin use. In the [lorazepam](#) group, somnolence (54.4%) was the most frequently occurring adverse effect. Of note, pregabalin was associated with a mean weight gain of 1.3 kg with the 150 mg/day dose and 2.2 kg with the 600 mg/day dose. [Lorazepam](#) was associated with a mean weight loss of 0.2 kg. [Lorazepam](#) was also associated with more withdrawal symptoms after 4 weeks of treatment (p=0.002) [4].

## 4.5.D) Burn - Pain

### 1) 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](#)

### 2) Summary:

[Lorazepam](#) potentiated opioid analgesia in patients with procedural burn pain in a double-blind, placebo-controlled study (n=79) [38].

### 3) Adult:

a) [Lorazepam](#) potentiated opioid analgesia in patients with procedural burn pain. In a double-blind, placebo-controlled study, 79 patients received either [lorazepam](#) 1 mg or placebo in addition to their opioid analgesia. Overall, [lorazepam](#) did not have a strong analgesic effect. However, patients who did have a high baseline pain rating, received significant pain relief (p less than 0.05). Trait anxiety did not predict patients responding to [lorazepam](#) [38].

## 4.5.E) Chemotherapy-induced nausea and vomiting; Prophylaxis

### 1) Overview

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

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

Recommendation: Adult, Class IIa; **Pediatric, Class IIa**

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

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

**2) Summary:**

[Lorazepam](#) orally or IV in combination with other antiemetics has been effective in preventing nausea and vomiting during [cancer](#) chemotherapy [26] [27] [28] [29].

**3) Adult:**

**a)** [Lorazepam](#) 3 mg orally combined with 2.5 mg IV [haloperidol](#) prior to [doxorubicin](#) or cisplatin infusion was effective in preventing nausea and vomiting in a majority of patients [26] [27].

**b)** [Lorazepam](#) 4 to 5 mg IV was added to [perphenazine](#) 5 mg orally and given to 7 patients receiving [dactinomycin](#), [doxorubicin](#), [cyclophosphamide](#), and [dacarbazine](#). Addition of [lorazepam](#) reduced vomiting to a maximum of 2 episodes in 6 of 7 patients [28].

**c)** The combination of [metoclopramide](#), [dexamethasone](#), [diphenhydramine](#), and [lorazepam](#) provided complete protection from nausea and vomiting in 48 of 50 and 42 of 50 patients treated with cisplatin, respectively. Five patients experienced 2 or fewer vomiting episodes, 2 patients had 3 to 5 emetic episodes, while 1 patient experienced 10 vomiting episodes. The antiemetic regimen included [metoclopramide](#) 3 mg/kg 30 minutes prior to and 90 minutes following cisplatin therapy, [dexamethasone](#) 20 mg and [diphenhydramine](#) 50 mg both IV 30 minutes prior to chemotherapy, along with [lorazepam](#) 1.25 mg orally 30 minutes prior to cisplatin administration. The authors stated when these results were compared with their previous experience, the use of [lorazepam](#) failed to provide additional benefits and was associated with higher toxicity (lethargy, sedation, [akathisia](#)) [29].

**4) Pediatric:**

**a)** [Lorazepam](#) 0.05 mg/kg (maximum, 2 mg) IV was reported effective in controlling [chemotherapy-induced nausea and vomiting](#) in children 2 to 15 years of age in an uncontrolled pilot study [30]. [Lorazepam](#) was administered intravenously over 20 minutes, 30 minutes prior to chemotherapy with agents producing moderate emetic effects ([doxorubicin](#), [dactinomycin](#), [cyclophosphamide](#), ifosfamide, nitrogen mustard, intrathecal [methotrexate](#), [cytarabine](#)). The drug was considered as effective or more effective than standard antiemetic therapy with phenothiazines and steroids, particularly in children over the age of 6 years.

**4.5.F] [Chemotherapy-induced nausea and vomiting](#); Treatment and Prophylaxis**

See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUSEA AND VOMITING

**4.5.G] [Dementia](#)**

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF [DEMENTIA](#)

**4.5.H] [Insomnia, due to anxiety or situational stress](#)**

FDA Labeled Indication

**1) Overview**



FDA Approval: Adult, yes; **Pediatric, yes (oral only; 12 years and 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 C

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

**2) Summary:**

Effective for the treatment of insomnia due to anxiety or transient situational stress [2] [3]

[Lorazepam](#) was associated with rebound symptoms, therefore other hypnotic agents with differing pharmacokinetic profiles might be preferable for [chronic insomnia](#) therapy [9].

[Lorazepam](#) is an effective hypnotic agent, however it is associated with hangover effects and performance decrements during the daytime [10] [11].

**3) Adult:**

a) [Lorazepam](#) 3 to 4 mg at bedtime was an effective hypnotic agent; however, hangover effects and performance decrements can occur during the daytime (especially during the first few days of treatment) and withdrawal insomnia has occurred [10] [11].

b) [Lorazepam](#) 0.5 milligram (mg) 3 times daily was equally effective as 1.5 mg at bedtime in the treatment of [chronic insomnia](#) when evaluated under short-term sleep laboratory conditions (n=12). Objective measurements revealed significantly decreased wake time, arousal index and nocturnal metabolic rate with increased sleep efficiency, while subjective ratings noted statistically improved sleep length. Although [lorazepam](#) did not adversely affect psychomotor performance, daytime symptoms related to [chronic insomnia](#), including tension/anxiety and confusion, tended to worsen at the end of the dosing interval (early morning for 3 times daily dosing, late evening for bedtime dosing). Because of these rebound symptoms, the authors concluded that other hypnotic agents with differing pharmacokinetic profiles might be preferable for [chronic insomnia](#) therapy [9].

**4.5.I) Premedication for anesthetic procedure**

FDA Labeled Indication

**1) Overview**

FDA Approval: Adult, yes (injection only); **Pediatric, no (.)**

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIa; **Pediatric, Class IIb**

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

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

**2) Summary:**

[Lorazepam](#) injection is indicated as [preanesthetic medication](#) to produce sedation (sleepiness or drowsiness), relief of anxiety, and a decreased ability to recall events related to the day of surgery [12]

There is insufficient data to support efficacy or to make dosage recommendations for preanesthetic sedation in children less than 18 years of age [12].

**3) Adult:**

a) Oral and sublingual [lorazepam](#) has been found to be a useful premedication for a variety of procedures such as [bronchoscopy](#) [13], [spinal anesthesia](#) [14], ophthalmic procedures [15], and in oral surgical patients [16] [17] [18]. It is also useful orally as an effective adjunct to [meperidine](#) in labor [19]. Comparable results with [diazepam](#) have been reported [20].

b) Sublingual [lorazepam](#) alone provided sufficient anxiolysis and sedation prior to [coronary artery bypass graft surgery](#) in a randomized, double-blind clinical trial involving 68 patients [21]. The addition of [morphine](#) and [perphenazine](#) resulted in elevated PaCO<sub>2</sub>, arterial [hemoglobin](#), desaturation, and potentially adverse hemodynamic changes. The increased level of sedation in the patients receiving additional [morphine](#) and [perphenazine](#) was judged as being not necessary for the prevention of [myocardial ischemia](#).

#### 4) Pediatric:

a) [Lorazepam](#) 0.05 mg/kg orally was an effective premedicant in children undergoing [plastic surgery](#) or ENT operations. In this study, [lorazepam](#) produced better amnesia than [diazepam](#) 0.25 mg/kg orally [22].

#### 1) Dental Sedation

a) Lorazepam in single oral doses of 0.5 or 1 mg was no more effective than placebo as premedication for apprehensive children (15 to 24 kg) before dental procedures [23].

### 4.5.J] Sedation

#### 1) Overview

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

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

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

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

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

#### 2) Summary:

[Lorazepam](#) administration, either as a continuous or intermittent intravenous infusion, is effective for the sedation of mechanically ventilated, critically ill patients [41]

Preferred agent for critically ill patients requiring prolonged sedation in the intensive care unit [42] [43]

Has been used as premedication prior to dental procedures in pediatric patients [23]

See Drug Consult reference: [PEDIATRIC SEDATION REGIMENS](#)

#### 3) Adult:

a) The advantages of [lorazepam](#) include its longer duration of action, less potential to cause hypotension, lower cost, and with prolonged administration results in more rapid awakening [42] [43]. [Lorazepam](#) may be administered as either intermittent intravenous bolus injections or as a continuous infusion.

### 4.5.K] Seizure

**1)) Overview**

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

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

Recommendation: Adult, Class IIa; Pediatric, **Class IIa**

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

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

**2)) Summary:**

IV [lorazepam](#) given upon arrival to the emergency room following witnessed generalized tonic-clonic seizures was shown to be effective in preventing recurrent alcohol-related seizures in a well-designed study of patients with known chronic alcohol abuse (n=186) [44].

Oral [lorazepam](#) increasing biweekly until seizures decreased or toxicity occurred, was an effective adjunct in controlling intractable partial complex seizures in a controlled clinical trial [45].

More studies are needed to define its role

**3)) Adult:**

**a))** [Lorazepam](#) 1 mg orally twice daily increasing biweekly until seizures decreased or toxicity occurred, was an effective adjunct in controlling intractable partial complex seizures in a controlled clinical trial. Optimal doses appeared to be 5 mg/day with corresponding plasma levels of 26 nanograms/mL [45].

**b))** IV [lorazepam](#) 2 mg given upon arrival to the emergency room following witnessed generalized tonic-clonic seizures was shown to be effective in preventing recurrent alcohol-related seizures. In a well-designed study, patients (n=186) with known chronic alcohol abuse that had consumed 1 or more alcoholic drinks in the previous 72 hours and experienced a generalized tonic-clonic seizure were randomized to receive either 2 mg of IV [lorazepam](#) (n=100) or normal saline (n=86). Patients were observed for 6 hours following medication administration or until a second seizure occurred. Three percent (n=3) of patients in the [lorazepam](#) group experienced a second seizure compared with 24% (n=21) of patients in the placebo group (p less than 0.001). Forty-two percent of the placebo group and 29% of the [lorazepam](#) group had emergency room visits that resulted in hospital admissions (p=0.02) [44].

**4)) Pediatric:**

**a))** Sublingual [lorazepam](#) 1 to 4 mg was effective in the treatment of serial seizures in 10 children in producing a good response in 8 and a partial response in 2. Onset of clinical effects was generally observed within 15 minutes (5 to 60 minutes). These data suggest that sublingual [lorazepam](#) may be useful in treating serial seizures [46].

**b))** [Lorazepam](#) was safe and effective for the treatment of [neonatal seizures](#), including those refractory to [phenobarbital](#) therapy, in a retrospective review of 13 neonates (7 males and 6 females; gestational ages 25 to 43 weeks) [47]. All patients had previously been treated with [phenobarbital](#) and/or [phenytoin](#), prior to the administration of [lorazepam](#). The dose of [lorazepam](#) ranged from 0.04 to 0.1 mg/kg (mean dose, 0.06 mg/kg). Seven neonates received a single dose and 6 received two or more doses. [Lorazepam](#) therapy resulted in clinical seizure control, for at least several hours, in 54% and was partially effective in another 23%. No side effects were directly attributed to the [lorazepam](#) therapy.

**c))** IV [lorazepam](#) was useful in the treatment of [neonatal seizures](#) (2 males and 5 females; gestational ages 30 to 43 weeks) in patients initially treated with [phenobarbital](#) and [phenytoin](#) [48]. [Lorazepam](#)

therapy was started at 0.05 mg/kg and administered intravenously over 2 to 5 minutes. Within 5 minutes of lorazepam administration cessation of all seizure activity was observed in all 7 patients. Seizure activity was totally abated in 71.4% of the patients and was controlled for at least 8 hours in the other 28.6%. No side effects could be directly attributed to lorazepam therapy. None of the patients experienced any respiratory depression following the administration of lorazepam, including the three who were on ventilators. Nor were there any problems associated with the propylene glycol and benzyl alcohol in the injectable.

#### 4.5.L] Seizure, drug-induced; Prophylaxis

##### 1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

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

##### 2) Summary:

No busulfan-induced seizures were reported when lorazepam was administered during high-dose busulfan therapy [49]

##### 3) Pediatric:

a) No patients developed seizures when lorazepam was administered concurrently with high-dose busulfan. Twenty-nine children ages 5 months to 19 years were given busulfan orally at 40 mg/m<sup>2</sup> or IV at 0.8 mg/kg every 6 hours for 12 total doses; dose was adjusted to maintain therapeutic concentrations. Intravenous or oral lorazepam 0.02 mg/kg to 0.05 mg/kg (maximum, 2 mg) was also given every six hours; it was administered 30 minutes prior to each busulfan dose and every six hours until four doses beyond the last busulfan dose. Individual dose adjustment was allowed for excessive sedation, with actual lorazepam doses ranging from 0.015 mg/kg to 0.045 mg/kg. No patients developed seizures and lorazepam was generally well tolerated, with exception of slight drowsiness reported in about half of the patients. One patient switched from lorazepam due to a possible drug-related skin allergy [49].

#### 4.5.M] Status epilepticus

FDA Labeled Indication

##### 1) Overview

FDA Approval: Adult, yes (injection only); Pediatric, no

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

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

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

##### 2) Summary:

Lorazepam is indicated in adults for the treatment of [status epilepticus](#) [12].

Lorazepam was easier to use, but no more effective, than [phenobarbital](#) or [diazepam](#) followed by [phenytoin](#) as initial therapy for [status epilepticus](#) (overt or subtle) in a multicenter, blinded study [31]. Lorazepam 4 mg IV was effective in the treatment of post-anoxic myoclonic [status epilepticus](#) in 6 patients following [cardiac arrest](#) [32] and was highly effective in the treatment of [status epilepticus](#) in another study in which seizures were controlled within 10 minutes in 89% of episodes [33].

Twenty-two of 25 patients had a successful response to [lorazepam](#) 4 or 8 mg IV during [status epilepticus](#) [34].

### 3) Adult:

a) [Lorazepam](#) was easier to use, but no more effective than, [phenobarbital](#) or [diazepam](#) followed by [phenytoin](#) as initial therapy for [status epilepticus](#) (overt or subtle). In a multicenter, blinded study, patients were randomized to receive either [lorazepam](#) 0.1 mg/kg (n=136), [phenytoin](#) 18 mg/kg (n=127), [phenobarbital](#) 15 mg/kg (n=124), or [diazepam](#) 0.15 mg/kg followed by [phenytoin](#) 18 mg/kg (n=131). Patients were classified as having either overt [generalized status epilepticus](#) or subtle [generalized convulsive status epilepticus](#). There was a significant difference in the frequency of success among the 4 treatments in those being treated for overt [status epilepticus](#) (p=0.02), but no differences in those treated for subtle [status epilepticus](#) (p=0.18). The 4 groups were actually not significantly different when an intention-to-treat analysis was used. Combining the 2 groups, [lorazepam](#) was successful as first-line treatment in 52.2%, [phenobarbital](#) in 49.2%, [diazepam/phenytoin](#) in 43.1%, and [phenytoin](#) alone in 36.8%. [Lorazepam](#) was effective significantly more often than [phenytoin](#) (p=0.001). [Lorazepam](#) also required the least time to infuse (p less than 0.001 in paired comparisons), and [phenytoin](#) took the longest (p less than 0.001) [31].

b) [Lorazepam](#) 4 mg IV was effective in the treatment of post-anoxic myoclonic [status epilepticus](#) in 6 patients following [cardiac arrest](#). Seizures were unresponsive to multiple anticonvulsants in 4 patients. Onset of seizure control occurred in approximately 4 minutes after [lorazepam](#) and no toxicity was observed [32].

c) [Lorazepam](#) 4 mg IV (2 mL of a 2 mg/mL solution over 4 minutes) was highly effective in the treatment of [status epilepticus](#) in one study, controlling seizures in 89% of episodes within 10 minutes [33].

d) Twenty-two of 25 patients had a successful response to [lorazepam](#) 4 or 8 mg IV during [status epilepticus](#). Seizures were controlled in 22 of 25 patients. A single seizure recurred in 5 of 22 patients. Transient respiratory arrest occurred in 1 patient. Most patients achieved seizure control at blood levels between 30 to 100 nanograms/mL. [Lorazepam](#) appears to be an effective and safe drug for controlling [status epilepticus](#), with a duration of control longer than that achieved with [diazepam](#) [34].

### 4) Pediatric:

a) [Lorazepam](#) was found to be effective in quickly terminating seizures (of various types) in over two-thirds of pediatric patients during an extensive retrospective study. Seventy-seven patients who received a total of 300 doses of [lorazepam](#) were included in the analysis. Therapy with [lorazepam](#) was considered successful if seizure activity subsided within 15 minutes of the intravenous dose. A single dose of [lorazepam](#) was successful in terminating seizures of all types 79% of the time. Successful [lorazepam](#) doses (median, 0.1 mg/kg) were similar to unsuccessful doses (median, 0.11 mg/kg), and there were no marked differences in the median doses used to treat the various seizure types. The median dose used in adolescents (0.07 mg/kg) was significantly lower than the median dose used in the 0 to 12-year-old age group (0.1 mg/kg; p equal to 0.0001). Partial seizures responded significantly better to [lorazepam](#) than generalized convulsive seizures (p=0.025). The initial pediatric dose recommended by the authors was

0.1 mg/kg IV up to a maximum single dose of 4 mg. Increasing or repeating the dose did not improve outcome. As the number of doses given in a sequential series increased, the response to lorazepam decreased. A longer interval between doses was associated with more frequent successes. Respiratory depression occurred infrequently after the first dose. Lorazepam was found to be equally effective and no more likely to cause adverse effects when used alone or when used after other anticonvulsants. [35].

b) Lorazepam terminated seizure activity in 25 of 31 (81%) pediatric patients (2 to 18 years old) during an open, multicenter study. Initially, lorazepam was administered 0.05 mg/kg IV at a rate of 1 mL/min, and was repeated up to two times if no response was observed after 15 minutes. Termination of seizure activity was obtained in 25 patients (81%) utilizing lorazepam. Seizure control was obtained in 60% of patients within 10 minutes and an additional 24% were controlled within 20 minutes. Duration of seizure control was 3 to 6 hours for 83% of the 23 patients whose seizures were controlled. The mean latency period was 10 minutes. No significant differences in response were observed for the different age groups. Lorazepam was most effective in controlling generalized status epilepticus. Termination of seizures was obtained in 92% (11/12) of these patients with a mean latency period of 6 minutes. Seizure termination was successful for 86% (6/7) of patients with partial elementary seizure epilepticus with a mean latency of 10 minutes. Seizure control was obtained in 67% (2/3) of patients with generalized absence seizures and in 75% (6/8) of patients with partial complex status epilepticus. Five patients were not controlled with lorazepam (1 with myoclonic seizures, 2 with generalized absence, 1 with partial complex seizure, and 1 with generalized convulsive seizure). Twenty patients required 1 injection, 7 received 2 injections, and 4 patients required 3 doses. No serious adverse reactions were noted [36].

#### 4.6] Comparative Efficacy / Evaluation With Other Therapies

##### 4.6.A] Alizapride

##### 4.6.A.1] Chemotherapy-induced nausea and vomiting

a) Intravenous alizapride (15 mg/kg given 30 minutes prior to cisplatin and 90 minutes after) plus intravenous dexamethasone/oral lorazepam was significantly less effective than a combination of intravenous metoclopramide (3 mg/kg 30 minutes before and 90 minutes after cisplatin) plus intravenous dexamethasone/oral lorazepam in controlling acute cisplatin-induced emesis in randomized study (n=145). Complete control of vomiting was observed in 32% and 50% of patients, respectively. Delayed vomiting (over 120 hours post-cisplatin) occurred with similar frequency in each group (60% and 69%, respectively) [363].

b) Similar findings were reported in a subsequent study by these investigators, with complete control of acute cisplatin-induced emesis occurring in 25% and 65% of patients receiving alizapride/dexamethasone/lorazepam and metoclopramide/dexamethasone/lorazepam, respectively [364]. In this study, treatment with oral alizapride plus intramuscular dexamethasone for 4 days post-cisplatin was less effective than oral metoclopramide/dexamethasone for controlling delayed emesis.

c) In a double-blind study (n=100), a combination of alizapride 3 mg/kg intravenously for 4 doses plus lorazepam 2.5 mg orally was significantly less effective than intravenous metoclopramide (1 mg/kg for 4 doses)/oral lorazepam (2.5 mg) in providing complete protection from emesis (11% versus 37%) induced by highly emetogenic chemotherapy regimens, including cisplatin. No significant difference between these regimens was observed for duration of nausea and vomiting, number of vomiting episodes, or adverse effects. In this study, alizapride/lorazepam and metoclopramide/lorazepam (each in lower doses) were equally effective with regard to complete control of vomiting and other parameters in patients receiving moderately emetogenic chemotherapeutic regimens [365].

##### 4.6.B] Alpidem



#### 4.6.B.1] Anxiety

a) Alpidem is as effective as [lorazepam](#) in the treatment of anxiety. Alpidem in flexible increasing doses (mean dose 227 mg/day) was compared with [lorazepam](#) (mean dose 4.3 mg/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 [345].

#### 4.6.C] [Amobarbital](#)

##### 4.6.C.1] Anxiety

a) [Lorazepam](#) 1.5 milligrams 3 times daily had a significantly better overall effect and was more effective than [amobarbital](#) 65 milligrams 3 times daily in reducing psychic anxiety, but there were no significant differences between [lorazepam](#) 0.75 milligram 3 times daily and [amobarbital](#) [296].

#### 4.6.D] [Bopindolol](#)

##### 4.6.D.1] Anxiety

a) [Bopindolol](#) was more effective than the benzodiazepine [lorazepam](#) or the barbiturate [butalbital](#) in alleviating pre-surgical anxiety. In a randomized, double-blind trial, patients were given [bopindolol](#) 1 milligram (mg) or 2 mg, [lorazepam](#) 2.5 mg, [butalbital](#) 75 mg, or placebo the day before surgery (20 patients in each group). At 3 separate times (prior to anti-anxiety treatment, the evening before surgery approximately 3 hours after drug administration, and the following morning prior to surgery) patients were evaluated for anxiety with a questionnaire and by a manual dexterity test. [Bopindolol](#) significantly reduced time required for the manual dexterity test game (p less than 0.01), while the time increased or decreased non-significantly in the other therapy groups. [Bopindolol](#) produced no significant increase in anxiety levels as determined by the questionnaire, while all other therapies were not significantly different than placebo. [Bopindolol](#) also had more favorable effects than the other therapies with regard to ease of falling asleep, night awakenings, and reawakening mood the day of surgery [297].

#### 4.6.E] [Bromazepam](#)

##### 4.6.E.1] Administration of medication - Preoperative care

a) Oral [bromazepam](#) 6 mg was as effective as oral [lorazepam](#) 2 mg as a premedicant prior to [gynecological surgery](#) in a controlled study involving 153 patients [300].

##### 4.6.E.2] [Anxiety neurosis](#)

a) [Bromazepam](#) and [lorazepam](#) were equally effective and superior to placebo in reducing anxiety scores in 61 outpatients receiving treatment for a [generalized anxiety disorder](#). All patients satisfied DSM-III criteria for generalized anxiety. In a well-designed trial, patients were assigned to [bromazepam](#) 12 to 18 mg/day, [lorazepam](#) 4 to 6 mg/day, or placebo. All patients received their total daily dose on a flexible 3 times a day regimen. The most common side effect of drowsiness was reported significantly more frequently in those receiving [lorazepam](#); depression, fatigue, and ataxia were evenly distributed between both drugs [298].



**b)** A double-blind, randomized, multicenter trial of 750 patients assessed the comparative efficacy of bromazepam and [lorazepam](#) for the treatment of anxiety [299]. Patients received bromazepam 3 mg or [lorazepam](#) 1 mg two times a day. Patients were treated for 7 to 14 days, discontinued at 7 days if no further treatment was required, or continued with options of altering the dose. Patients evaluated their response to treatment by use of a questionnaire. Although the doctors' global assessment significantly rated more patients to be improved in the bromazepam group (85% versus 77%), both drugs were comparable in their ability to improve the individual signs and symptoms of anxiety. The occurrence of unwanted effects was similar for both groups.

#### **4.6.E.3] Withdrawal sign or symptom**

**a)** Sixty-eight patients with [benzodiazepine dependence](#) were randomly treated with [lorazepam](#), [diazepam](#), or bromazepam in doses equivalent to those of their original benzodiazepine. Medication was tapered by 25% of the original dose every 2 weeks until the drug had been discontinued. Withdrawal symptoms were similar in all groups although a higher percentage of the lorazepam-treated patients dropped out of the study. Withdrawal symptoms were more severe in patients with personality disorders or in those who had taken benzodiazepines for more than 5 years [301].

### **4.6.F] [Buspirone](#)**

#### **4.6.F.1] Anxiety**

**a)** Few significant differences were observed between [busPIRone](#) (15.2 milligrams (mg)/day) and [lorazepam](#) (3.5 mg/day) in a 4-week, multicenter, randomized, double-blind, parallel-group study of 113 patients fulfilling Diagnostic Style Manual-III criteria for [generalized anxiety disorder](#). Patients had a Hamilton Rating Scale for Anxiety (HRSA) score higher than 18. Both treatments improved anxiety ( $p = 0.0001$ ) according to HRSA scores, 100 mm Visual Analogue Scale, Clinical Global Impression Scale (CGIS) and Clinical Global Self Rating Scale (CGSRS). [Lorazepam](#) showed significantly higher improvement in HRSA score ( $p$  less than 0.05) and CGIS ( $p = 0.002$ ) than [busPIRone](#) after 1 week. Adverse effects were reported in 38% of [busPIRone](#) patients (dizziness, nausea and vomiting, headache) versus 27% in the [lorazepam](#) group (sleepiness, dizziness, fatigue) [309].

#### **4.6.F.2] Efficacy**

**a)** A small, randomized, double-blind, 4-week study of 14 patients (6 males, 8 females; mean age 48 years) fulfilling Diagnostic Style Manual- III criteria for [generalized anxiety disorder](#) compared the effect of [busPIRone](#) 30 milligrams (mg)/day and [lorazepam](#) 6 mg/day on electroencephalographic spectral power. [BusPIRone](#) showed a significantly ( $p$  less than 0.05) increased output of slow frequencies (delta and theta) and decreased fronto-central beta-2 spectral power. Clinical effects were not studied [310].

### **4.6.G] [Butalbital](#)**

#### **4.6.G.1] Anxiety about treatment, Preoperative**

**a)** [Butalbital](#) was compared with [lorazepam](#) in preventing preoperative anxiety (Chicrichetti et al, 1985). Patients were randomized to receive 75 mg [butalbital](#) or 2.5 mg [lorazepam](#) the day before surgery. Twenty patient were assigned to each group. [Lorazepam](#) was significantly better in reducing anxiety when measured on the morning before surgery (approximately 16 hours after giving the drugs). Ease of falling asleep and night awakenings the night before surgery were similar for both groups. Mood on awakening was slightly better for the [lorazepam](#) group (statistical significance not given).

#### 4.6.H] Carbamazepine

##### 4.6.H.1] Alcohol withdrawal syndrome

a) Carbamazepine and lorazepam were equally efficacious for the treatment of symptoms associated with alcohol withdrawal, but carbamazepine was superior for preventing rebound withdrawal symptoms and for reducing post-treatment drinking, especially in those patients with a history of multiple withdrawals. In a randomized, double-blind trial, 136 treatment-seeking patients with alcohol dependence were stratified according to number of previous withdrawal experiences (2 or more vs less than 2) prior to randomization to treatment with carbamazepine on a 5-day fixed dose taper, starting with 600 to 800 milligrams (mg) on day 1 and tapering to 200 mg as a single dose on day 5, or lorazepam, 6 to 8 mg on day 1 and tapering to a single 2 mg dose on day 5. Prior research had determined the equivalency of the dosages of carbamazepine and lorazepam. Patients with 2 or more previous detoxifications had significantly higher scores on the CIWA-Ar (Clinical Institute Withdrawal Assessment for Alcohol-Revised) throughout treatment and during the post-treatment follow-up (days 7 to 12) than did patients with fewer than 2 previous detoxifications. The mean number of drinks per day during post-treatment was similar for carbamazepine-treated and lorazepam-treated patients who had 0 or 1 prior detoxifications, whereas, among those with more than 2 prior detoxifications, the average daily consumption was 5 drinks for the lorazepam group and 1 for the carbamazepine group ( $p=0.004$ ). The relative risk of having a first drink was 3 times higher for the lorazepam group than for the carbamazepine group. Twenty percent of carbamazepine-treated patients and 1.3% of lorazepam-treated patients complained of pruritus (but not with rash). Seven percent of the carbamazepine group and 23% of the lorazepam group showed signs of dizziness, incoordination, light-headedness, and drowsiness, which they themselves did not recognize [311].

#### 4.6.I] Chlordiazepoxide Hydrochloride

##### 4.6.I.1] Alcohol withdrawal syndrome

a) Five days of treatment with lorazepam compared with chlordiazepoxide significantly decreased symptoms of alcohol withdrawal within 48 hours (improvement in Clinical Institute Assessment for Alcohol-revised [CIWA-Ar] score by 70.4% vs 54.8%) and decreased the duration of withdrawal symptoms (5.6 vs 6.7 days) in a double-blind study in male inpatients of a de-addiction ward ( $N=108$ ). Overall, alcoholic liver disease was present in 47.6%, delirium was present in 22.3%, and 20.4% developed withdrawal seizures. Depending on baseline CIWA-Ar score, patients received either lorazepam 6 or 8 mg, or chlordiazepoxide 150 or 200 mg. The dose was tapered by 20% daily and discontinued by day 5 [351].

#### 4.6.J] Clobazam

##### 4.6.J.1] Anxiety

a) One study reported the comparable efficacy of lorazepam 3 milligrams daily and clobazam 30 milligrams daily in treatment of anxiety in outpatients for a period of four weeks. Anxiety scores deteriorated within the first week after withdrawal of lorazepam but not with clobazam, which is to be expected due to the shorter elimination half-life of lorazepam. It does not appear that clobazam offers any advantage over lorazepam in the treatment of anxiety [308].

#### 4.6.K] Clonazepam

##### 4.6.K.1] Mania

a) Lorazepam was superior to clonazepam in treating acute mania in 21 patients in a well designed study. A significant improvement in mood, logorrhea, insight, grandiosity, hostility, and excitement was observed

in 11 patients receiving lorazepam 12.5 milligrams (mean) in 3 divided doses compared to 10 patients treated with clonazepam 12.75 milligrams (mean) in 3 divided doses. By day 14, 61.5% of the lorazepam-treated patients responded to treatment, with 38.5% of patients achieving remission, compared with a 18.2% response rate and a 0% remission rate with clonazepam. Following 14 days of monotherapy, lithium was added to the regimen and 4 patients in the clonazepam-treated group achieved remission along with 3 additional patients in the lorazepam-treated group on day 28 [360].

#### 4.6.K.2] Status epilepticus

a) Intravenous lorazepam was compared with clonazepam in 61 patients with status epilepticus. Lorazepam alone 4 to 10 milligrams, clonazepam 1 milligram, alone or both lorazepam and clonazepam at different times were administered to a total of 61 patients in status epilepticus. In comparing the overall EEG and clinical results, lorazepam produced greater EEG improvement, while clonazepam provided a greater improvement in clinical symptoms. The only adverse effect associated with lorazepam administration was a change in the degree of alertness, persisting up to 24 hours. Drowsiness after clonazepam therapy was brief, persisting only 3 to 4 hours. However, 4 clonazepam-treated patients developed respiratory difficulties [361].

#### 4.6.L] Clorazepate

##### 1) Efficacy

a) The results of 2 studies show that lorazepam has greater amnestic effect than clorazepate, diazepam, or placebo in young, healthy adults [315] [316]. 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 [315]. 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 [316]. 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.M] Clothiapine

##### 4.6.M.1] Aggressive behavior

a) When added to oral haloperidol 10 milligrams (mg), intramuscular lorazepam 4 mg exhibited similar efficacy and superior tolerability as compared to intramuscular clothiapine 40 mg in the treatment of behaviorally disturbed patients admitted to an inpatient psychiatric unit in a controlled study (n=59). Diagnoses of subjects included psychosis associated with substance abuse, delusional disorder, schizophrenia, or bipolar disorder. Both adjuvant therapies, given as frequently as every 6 hours when needed, resulted in statistically equivalent onset and degree of improvements in the Brief Psychiatric Rating Scale and Overt Aggression Scale over the first week of hospitalization versus baseline values. The only between-group difference occurred in the Simpson Angus Scale, a measure of extrapyramidal adverse effects, which favored lorazepam [362].

#### 4.6.N] Delorazepam

##### 4.6.N.1] Anxiety

a) In a double-blind, placebo-controlled, cross-over study, [lorazepam](#) (0.9 milligram (mg) in three daily doses) was compared with delorazepam (0.9 mg in three daily doses) and placebo in the treatment of [generalized anxiety disorders](#) according to DSM III-R criteria. According to the total Zung Self-Rating Anxiety Scale score, delorazepam was more effective than [lorazepam](#) in the first two weeks of treatment. Efficacy and adverse effects correlated well with the pharmacokinetic properties of two drugs; a long-acting benzodiazepine such as delorazepam appears to be preferable to a short-acting one ([lorazepam](#)) for anxiolysis [312].

b) In a double-blind, cross-over study, [lorazepam](#) was compared to delorazepam in the treatment of 20 female neurotic inpatients. Statistically greater efficacy was reported for delorazepam after the first week and at the end of the two-week treatment period according to the Hamilton Rating Scale for Anxiety and [Overall and Gorham's brief psychiatric rating scale](#) [313]. Larger and longer randomized studies are needed to better evaluate the role of two drugs in the treatment of anxiety disorders.

#### 4.6.O] [Dexmedetomidine Hydrochloride](#)

##### 4.6.O.1] Sedation for a mechanically ventilated patient

a) In the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study, treatment with [dexmedetomidine](#) led to a higher percentage of days at a target level of sedation with significantly more [delirium](#)- and coma-free days compared with [lorazepam](#) in mechanically ventilated patients. In this randomized, double-blind study, patients in the medical or surgical intensive care unit (ICU) who required mechanical ventilation for longer than 24 hours (hr) received [dexmedetomidine](#) (infusion bag concentration, 0.15 microgram/kilogram/milliliter (mcg/kg/mL)) starting at 0.15 mcg/kg/hr to a maximum of 1.5 mcg/kg/hr (n=52; median age, 60 years (yr); interquartile range (IQR), 49 to 65 yr) or [lorazepam](#) (infusion bag concentration, 1 milligram (mg)/mL) starting at 1 mL/hr and titrated to a maximum rate of 10 mL/hr (n=51; median age, 59 yr; IQR, 45 to 67 yr) to achieve sedation goals using the Richmond Agitation Sedation Scale (RASS) (median infusion rate: [dexmedetomidine](#) arm, 0.74 mcg/kg/hr (IQR, 0.39 to 1.04 mcg/kg/hr); [lorazepam](#) arm, 3 mg/hr (IQR, 2.2 to 6.6 mg/hr)). Patients could receive treatment until [extubation](#) or for a maximum time of 120 hr. Intermittent [fentanyl](#) doses (for signs and symptoms of pain), a [fentanyl](#) infusion (for inadequate sedation or for pain requiring frequent [fentanyl](#) intermittent doses), and [propofol](#) 25 to 50 mg bolus doses (for severe agitation) were allowed during the study period. [Delirium](#) was diagnosed using the RASS (score of -3 or greater) and the Confusion Assessment Method for the ICU (CAM-ICU) instrument for 12 days. Coma was diagnosed in patients having a RASS score of -4 or -5. The composite endpoint of [delirium](#)- and coma-free days (primary endpoint), defined as the number of days in a 12-day period following enrollment in which a patient was alive with no [delirium](#) or coma, was significantly (p=0.01) improved with [dexmedetomidine](#) (median, 7 days; IQR, 1 to 10 days) compared with [lorazepam](#) (median, 3 days; IQR, 1 to 6 days). A higher percentage of days was spent at a target level of sedation (or within 1 RASS point of goal) in dexmedetomidine-treated patients compared with lorazepam-treated patients for both nurse ([dexmedetomidine](#) arm: 80% (IQR, 58% to 100%); [lorazepam](#) arm, 67% (IQR, 48 to 83%); p=0.04) and physician ([dexmedetomidine](#) arm: 67% (IQR, 50% to 85%); [lorazepam](#) arm, 55% (IQR, 8 to 67%); p=0.008) sedation goals. No significant differences were found between the 2 treatment arms for the secondary study endpoints of ICU length of stay (p=0.92), mechanical ventilator-free days from study day 1 to 28 (p=0.22), 28-day mortality (p=0.18), and 12-month survival (p=0.48). Significantly (p=0.03) more patients experienced [sinus bradycardia](#) (heart rate less than 60 beats/minute) in the [dexmedetomidine](#) arm (n=9; 17%) compared with the [lorazepam](#) arm (n=2; 4%) [306].

#### 4.6.P] Diazepam

##### 4.6.P.1] Administration of medication - Preoperative care

a) Intravenous lorazepam 2 and 4 milligrams was compared with intravenous diazepam 10 and 20 milligrams in 120 preoperative patients [331]. They evaluated the sedative, antianxiety, and amnestic effects produced by these 2 benzodiazepines. This data, although subjective and not statistically analyzed, suggest that intravenous lorazepam is at least as effective as diazepam in relieving preoperative anxiety and producing sedation. The amnestic effects produced by lorazepam are slightly delayed when compared to diazepam, but of similar magnitude.

##### 4.6.P.2] Anxiety

a) In the treatment of anxiety, most studies indicate that both diazepam and lorazepam are equally [321] [322] [323] [324] [325]. Marginal differences in terms of efficacy on specific parameters (Hamilton Rating Scale) and side effects have been reported, but do not appear to be statically significant [321] [323]. Lorazepam is more likely to impair memory recall in patients undergoing surgery when used as an intravenous premedication [326]. In patients with moderate to severe anxiety, lorazepam in doses of 1 to 6 mg/day for a duration of 6 months results in a greater improvement of symptoms (anxiety, tension, insomnia, psychic and somatic cluster) than diazepam [327]. However, due to study design (not placebo controlled or cross-over) the validity of the results may be questionable.

b) In comparative trials, lorazepam has been as effective or superior to diazepam in the treatment of anxiety [322] [328] [329]. A double-blind study was conducted involving 73 patients suffering from uncomplicated anxiety states as defined by the Glossary of Mental Disorders [328]. Lorazepam was compared with both diazepam and placebo. All medications were given three times daily. The Hamilton Rating Scale was used to assess each patient's emotional status. Results were analyzed using Dunnett's statistical test and compared the group to both the lorazepam and diazepam groups at one and six weeks. The diazepam-treated group and all lorazepam-treated groups, except lorazepam 0.5 milligram three times a day (total daily dose 1.5 mg), improved significantly after one week. The fact that diazepam was statistically no better than placebo after 6 weeks of therapy is unexplained. However, the lorazepam-treated group continued to maintain significant improvement when compared with placebo at six weeks.

c) Lorazepam 0.05 milligram/kilogram intramuscularly (IM) was effective as diazepam 0.14 milligram/kilogram IM in the treatment of anxiety neurosis; however, lorazepam was superior to diazepam in certain cluster scores, including the Obsessive Compulsive Phobic Cluster of the Wittenborn Psychiatric Rating Scale [330].

##### 4.6.P.3] Status epilepticus

a) SUMMARY: Lorazepam and diazepam are equally effective in the treatment of status epilepticus. Lorazepam does, however, have a longer duration of antiseizure effect than diazepam (12 to 24 hours versus 15 to 30 minutes, respectively) [332].

b) Lorazepam was easier to use but no more effective than phenobarbital, or diazepam followed by phenytoin as initial therapy for status epilepticus (overt or subtle) [333]. In a multi-center, blinded study, patients were randomized to receive either lorazepam 0.1 milligrams/kilogram (mg/kg) (n=136), phenytoin 18 mg/kg (n=127), phenobarbital 15 mg/kg (n=124), or diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg (n=131). Patients were classified as having either overt generalized status epilepticus or subtle generalized convulsive status epilepticus. There was a significant difference in the frequency of success among the 4 treatments in those being treated for overt status epilepticus (p=0.02), but no differences in those treated for subtle status epilepticus (p=0.18). The 4 groups were actually not significantly different when an intention to treat analysis was used. Combining the 2 groups, lorazepam was successful as first-line



treatment in 52.2%, [phenobarbital](#) in 49.2%, [diazepam/phenytoin](#) in 43.1%, and [phenytoin](#) alone in 36.8%. [Lorazepam](#) was effective significantly more often than [phenytoin](#) ( $p=0.001$ ). [Lorazepam](#) also required the least time to infuse ( $p$  less than 0.001 in paired comparisons), and [phenytoin](#) took the longest ( $p$  less than 0.001).

c) [Lorazepam](#) was compared with [diazepam](#) in 70 episodes of [status epilepticus](#) in 69 patients [334]. Patients received 10 milligrams intravenous (IV) [diazepam](#) or 4 milligrams IV [lorazepam](#) in double-blind, randomized fashion (2 mL of either drug). A second 2 mL dose was administered if seizures continued or recurred after 10 minutes. Convulsions were controlled in 89% of lorazepam-treated episodes and 76% of [diazepam](#) episodes (not statistically significant). Adverse effects were similar.

d) In a retrospective study, intravenous [lorazepam](#) was compared with intravenous [diazepam](#) in the treatment of [status epilepticus](#) in children aged 2 weeks to 18 years [335]. Both drugs were reported to be similarly effective in controlling seizures. The mean dose of [diazepam](#) required to control seizure activity was  $0.38 \pm 0.21$  milligram/kilogram (range, 0.09 to 0.71 mg/kg). The mean dose of [lorazepam](#) required for seizure control was  $0.11 \pm 0.05$  milligram/kilogram (range, 0.03 to 0.22 mg/kg). Overall, seizure control was achieved in 11 of 16 diazepam-treated patients (69%) and in 18 of 22 lorazepam-treated patients (82%). Adverse effects were similar with both agents; [respiratory depression](#) requiring intubation occurred in 5 of 14 diazepam-treated patients (36%) and in 6 of 24 lorazepam-treated patients (25%). In the lorazepam-treated group, only children younger than 2 years of age required intubation due to [respiratory depression](#).

#### 4.6.Q] [Dimenhydrinate](#)

##### 4.6.Q.1] Vertigo

a) A double-blind study comparing the efficacy of [dimenhydrinate](#) and [lorazepam](#) for treating vertigo was inconclusive; however, [dimenhydrinate](#) was less sedating than [lorazepam](#). Patients presenting with the symptoms of vertigo ( $n=74$ ) were treated with either intravenous [lorazepam](#) 2 milligrams (mg) or intravenous [dimenhydrinate](#) 50 mg. After treatment, scores for vertigo under 4 conditions (ambulation, lying, sitting, and when turning the head from side to side) and nausea were consistently lower in the [dimenhydrinate](#) group, but baseline scores were also lower in that group, and score changes with [dimenhydrinate](#) treatment were not statistically different from those with [lorazepam](#) treatment. Drowsiness was noted twice as often in the [lorazepam](#) group as in the [dimenhydrinate](#) group [336].

#### 4.6.R] [Diphenhydramine](#)

##### 4.6.R.1] Chemotherapy-induced nausea and vomiting

a) [Lorazepam](#) was as effective as [diphenhydramine](#) for relieving chemotherapy-induced emesis. Two studies indicated that intravenous [lorazepam](#) 1.5 mg/m<sup>2</sup> and intravenous [diphenhydramine](#) 50 mg in combination with [metoclopramide](#) plus [dexamethasone](#) were well-tolerated and effective for reducing the nausea and vomiting associated with cisplatin. However, [lorazepam](#) was more effective for relieving anxiety and restlessness from the chemotherapy [347] [348]. [Lorazepam](#) appears to offer no benefit over [diphenhydramine](#). [Moderate sedation](#) was found in 10% (5/50) of the patients [349].

#### 4.6.S] [Flunitrazepam](#)

##### 4.6.S.1] Administration of medication - Preoperative care

a) Flunitrazepam 2 mg and [lorazepam](#) 2.5 mg, each given the night before surgery and again on the morning of surgery, were similarly effective as oral premedicants in patients undergoing [gynecological surgery](#) in a double-blind study. Although sedation was more pronounced with flunitrazepam, no significant difference was observed regarding apprehension, sleep quality, excitement, dizziness, emetic

effects, or blood pressure changes. Combined results of all evaluation parameters revealed no difference between lorazepam and flunitrazepam [314].

#### 4.6.T] Flurazepam

##### 4.6.T.1] Insomnia

a) A double-blind, placebo-controlled, crossover study involving 15 patients and 15 controls compared oral lorazepam 2 to 4 milligrams as a single dose with flurazepam in the treatment of insomnia [337]. Results indicated that lorazepam in a dose of 2 to 4 mg was significantly superior to placebo and flurazepam 15 milligrams based on onset, duration, depth of sleep, frequency of awakening, and subjective satisfaction. However, the 2 and 4 mg dose of lorazepam was equivalent to flurazepam 30 mg. There appeared to be no significant difference between the 2 and 4 mg doses of lorazepam.

b) Hypnotic efficacy and safety of 3 weeks of daily doses of 2 milligrams lorazepam or 30 milligrams flurazepam were compared in a double-blind crossover study in 8 chronic insomniacs [338]. Subjects were monitored in the sleep laboratory twice weekly for a total of 25 nights. Subjective estimates of sleep, vigilance tests, and adverse effects were recorded throughout the study. It was found that neither drug impaired REM sleep or vigilance test performance. Side effects of grogginess were expected. Both lorazepam 2 mg and flurazepam 30 mg were found to be effective and safe. Lorazepam had more favorable effects on sleep than did flurazepam.

#### 4.6.U] Fluvoxamine

##### 4.6.U.1] Depression

a) Fluvoxamine (50 to 300 mg/d) was compared with lorazepam (1 to 6 mg/d) in a multi-center, double-blind, parallel group study in 112 general practice patients with mixed anxiety and depression. Response was assessed over a 6-week period using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Anxiety Scale (CAS). There were no significant differences between treatments at any point except in an elderly subgroup where anxiety improved more rapidly with lorazepam. There were significant improvements in MADRS and CAS, and global ratings compared with baseline at all subsequent assessments. Lorazepam produced more sedation while fluvoxamine produced more nausea and vomiting [355].

#### 4.6.V] Gabapentin

##### 4.6.V.1] Alcohol withdrawal syndrome

a) In a randomized, double-blind trial (n=100), high-dose gabapentin led to significantly lower Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scores compared with lorazepam in outpatients with alcohol withdrawal. Patients with alcohol dependence and withdrawal (using the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria), a Mini-Mental State Exam score of 26 or higher, and a CIWA-Ar score of 10 or greater who volunteered for treatment of alcohol withdrawal received 4 days of gabapentin or lorazepam. One of the following 3 fixed-dose tapers of gabapentin were administered: 1) 200 milligrams (mg) 3 times daily for 3 days, then 200 mg twice daily on day 4 (600 mg arm; n=16); 2) 300 mg 3 times daily for 3 days, then 300 mg twice daily on day 4 (low-dose arm; n=28; mean age, 38.4 +/- 1.82 years (yr); mean drinks/day in previously 14 days, 12.1 +/- 1.16 drinks); or 3) 400 mg 3 times daily for 3 days, then 400 mg twice daily on day 4 (high-dose arm; n=28; mean age, 40.5 +/- 2.25 yr; mean drinks/day in previously 14 days, 16.8 +/- 2.18 drinks); however, the 600 mg arm was discontinued after one near syncopal event and 2 patient-reported seizure-like episodes occurred and patients in this arm were not included in the final analysis. The lorazepam fixed-dose taper was administered as 2 mg 3 times daily for 3 days, then 2 mg twice daily on day 4 (n=28; mean age, 39.1 +/-



1.83 yr; mean drinks/day in previously 14 days, 11.4 +/- 1.11 drinks). CIWA-Ar assessment was performed daily during the medication phase and on 1, 2, and 7 days posttreatment (follow-up phase). All patients received oral thiamine 100 mg daily for 12 days. Patients could take blinded, prepackaged supplemental [gabapentin](#) or [lorazepam](#) as needed on days 1 to 4 to treat subjective symptoms of alcohol withdrawal and there were no significant differences ( $p=0.75$ ) in supplemental medication use between [gabapentin](#) and lorazepam-treated patients. The mean CIWA-Ar score was significantly lower in the high-dose [gabapentin](#) arm but not the low-dose [gabapentin](#) arm compared with the [lorazepam](#) arm during the medication phase ([gabapentin](#): low-dose, 4.52 +/- 39 (standard error (SE)); high-dose, 3.14 +/- 0.37 (SE); [lorazepam](#): 4.26 +/- 0.38 (SE); high-dose [gabapentin](#) versus (vs) [lorazepam](#)  $p$  less than 0.05) and the follow-up phase ([gabapentin](#): low-dose, 1.79 +/- 0.32 (SE); high-dose, 1.03 +/- 0.31 (SE); [lorazepam](#): 2.53 +/- 0.31 (SE); high-dose [gabapentin](#) vs [lorazepam](#)  $p$  less than 0.01). Mean alcohol craving scores (evaluated on a visual analog scale of zero millimeters (mm) (no discomfort) to 100 mm (greatest discomfort)) were significantly ( $p$  less than 0.05) lower in patients who received [gabapentin](#) ([gabapentin](#): low-dose, 29.19 +/- 5 (SE); high-dose, 28.73 +/- 4.6 (SE)) compared with [lorazepam](#) (42.7 +/- 4.7 (SE)) during the medication phase; however, alcohol craving scores were not significantly different between the groups during the follow-up phase ([gabapentin](#): low-dose, 13.9 +/- 5.3 (SE); high-dose, 20.4 +/- 4.8 (SE); [lorazepam](#): 20.8 +/- 4.9 (SE)). Mean anxiety scores (evaluated using the Zung Anxiety Scale) were significantly ( $p$  less than 0.05) lower in patients who received [gabapentin](#) ([gabapentin](#): low-dose, 32.11 +/- 1.74 (SE); high-dose, 31.89 +/- 1.6 (SE)) compared with [lorazepam](#) (36.98 +/- 1.5 (SE)) during the medication phase and the mean anxiety score was significantly ( $p$  less than 0.01) improved in the high-dose [gabapentin](#) arm but not the low-dose [gabapentin](#) arm compared with [lorazepam](#) arm during the follow-up phase ([gabapentin](#): low-dose, 31.25 +/- 1.3 (SE); high-dose, 28.8 +/- 1.2 (SE); [lorazepam](#): 33.9 +/- 1.1 (SE)). During the medication phase, patients in the low-dose [gabapentin](#) arm had significantly ( $p$  less than 0.01) improved [Beck Depression Inventory](#) (BDI) scores and patients in the high-dose [gabapentin](#) arm had significantly ( $p$  less than 0.05) improved sleep scores evaluated using the Epworth Sleepiness Scale compared with patients in the [lorazepam](#) arm. The incidence of patient-reported adverse effects did not differ between the [gabapentin](#) and [lorazepam](#) arms ( $p=0.74$ ) [305].

#### 4.6.W] [Haloperidol](#)

##### 4.6.W.1] Agitation - [Psychotic disorder](#)

a) The combination of [haloperidol](#) and [lorazepam](#) was suggested to be more effective than [lorazepam](#) alone in agitated patients presenting to the psychiatric emergency service [318]. Patients who met clinical criteria for the use of chemical restraints and had a minimum score of 4 on the Overt Aggression Scale received either [lorazepam](#) 2 milligrams (mg) ( $n=11$ ) or [haloperidol](#) 5 mg and [lorazepam](#) 2 mg ( $n=9$ ). Combination therapy was significantly better than [lorazepam](#) alone after 1 hour according to the Overt Aggression Scale and the visual analog scale ( $p$  less than 0.05). However, on the Clinical Global Impressions severity scale, the comparison was not significant. With repeated measures of analyses of variance, both groups improved over time.

b) Repeated doses of either [lorazepam](#) 2 milligrams or [haloperidol](#) 5 milligrams were equally effective for the early treatment of acute agitation in psychotic patients [319]. In a double-blind, randomized study, 98 patients received either intramuscular [lorazepam](#), [haloperidol](#), or both. Patients received 1 to 6 injections in a 12-hour period depending upon clinical need. Effective symptom reduction was achieved in each treatment group with significant decreases from baseline at every hourly evaluation ( $p$  less than 0.01). Mean differences on the Agitated Behavior Scale and modified Brief Psychiatric Rating Scale suggested that tranquilization was most rapid in patients receiving the combination therapy ( $p$  less than 0.05).

##### 4.6.W.2] [Delirium](#)

a) **Chlorpromazine** (n=13) and **haloperidol** (n=11) were effective and had few side effects in the treatment of **delirium** in AIDS patients in a double-blind study; **lorazepam** (n=6) was not effective and was associated with adverse effects [317]. Average doses for the first 24 hours of treatment were **lorazepam** 3 mg, **chlorpromazine** 50 mg, and **haloperidol** 1.4 mg. There was significant improvement in the 2 neuroleptic-treated groups in the first 24 hours as measured by the **Delirium** Rating Scale scores (p less than 0.001 for both groups). Very little further improvement was seen after day 2. **Delirium** symptoms did not improve in the lorazepam-treated group. Cognitive status as measured by the Mini-Mental State scale improved in the **chlorpromazine** group (p less than 0.001) and **haloperidol** group (NS), but did not improve in the **lorazepam** group. Few extrapyramidal side effects were associated with either neuroleptic drug, but all lorazepam-treated patients developed adverse effects that led to the removal of this drug from the protocol. Breitbart et al recommend further study to confirm their finding that early intervention with low-dose neuroleptics is effective in managing **delirium** in AIDS patients.

#### 4.6.X] Ketazolam

##### 4.6.X.1] Anxiety

a) **Lorazepam** 1 mg TID was compared to ketazolam 30 mg HS in 60 patients with moderate to severe anxiety. Results indicated that ketazolam was equal to **lorazepam** at week 1, week 2, and overall [344].

#### 4.6.Y] Methaqualone

##### 1) Adverse Effects

a) Methaqualone was determined to be more euphoriant than **alprazolam**, **lorazepam**, and **diazepam** compared with placebo as determined by the Addiction Research Center Inventory and 2 other scales designed to assess abuse potential and sedative intoxication in 30 recreational drug users of college age [350]. The randomized, double-blind study was carried out over a 5-week period with all volunteers receiving single doses of **alprazolam** 2 mg, **lorazepam** 4 mg, methaqualone 300 mg, **diazepam** 20 mg, and placebo. At 1 hour after drug administration, methaqualone produced significantly more euphoria than **alprazolam** or placebo. **Diazepam** and **lorazepam** were more euphoriant than placebo, but not significantly less than methaqualone; however, at 2 hours methaqualone alone was shown to be significantly more euphoric than any other treatment, none of which differed from placebo. The sedation caused by methaqualone was less than that of **alprazolam**, **lorazepam**, and **diazepam**.

#### 4.6.Z] Methylprednisolone

##### 4.6.Z.1] Chemotherapy-induced nausea and vomiting

a) **LORAZEPAM** was more effective for reducing nausea and vomiting in patients receiving cisplatin-containing chemotherapy than **OXAZEPAM** or **methylPREDNISolone**. Eighty-five patients completed at least 2 of 3 consecutive chemotherapy regimens containing the same dose of cisplatin each time. The patients received single doses of **lorazepam** 2.5 mg/square meter, **oxazepam** 60 mg, and intravenous **methylPREDNISolone** 500 mg prior to chemotherapy on 3 separate occasions. **Lorazepam** reduced the incidence of vomiting and caused more effective amnesia than either **oxazepam** or **methylPREDNISolone** [320].

#### 4.6.AA] Metoclopramide

##### 4.6.AA.1] Chemotherapy-induced nausea and vomiting

a) **Metoclopramide** alone was compared with a combination of **metoclopramide** plus **lorazepam** for controlling nausea and vomiting secondary to cisplatin chemotherapy in a randomized, double-blind

study involving 64 patients [339]. The patients were randomly assigned to receive either intravenous [metoclopramide](#) 2 mg/kg alone 30 minutes prior to chemotherapy and 1.5, 3.5, and 5.5 hours after chemotherapy or the same doses in combination with intravenous [lorazepam](#) 2 mg/m(2) 30 minutes prior to chemotherapy. In this study, patients received cisplatin primarily in combination with either [etoposide](#), [5-fluorouracil](#), or [doxorubicin](#). Vomiting episodes were significantly less with the combination as compared to [metoclopramide](#) alone; no nausea or vomiting episodes were observed in 44% of patients receiving the combination as compared to 22% receiving [metoclopramide](#) alone. Sedation and amnesia occurred more frequently with the [lorazepam](#) combination. Extrapyrimal reactions ([dystonia](#)) were observed in 14% of patients receiving [metoclopramide](#) alone, however [dystonia](#) was not observed in any patient receiving [lorazepam](#), suggesting that [lorazepam](#) may have a role in controlling the extrapyramidal adverse effects of [metoclopramide](#).

**b)** A high-dose [metoclopramide](#) and [lorazepam](#) regimen was superior to a combination of [prochlorperazine](#) and [lorazepam](#) in controlling emesis in patients receiving cisplatin and non-cisplatin chemotherapy [340]. All patients received [lorazepam](#) 0.05 mg/kg PO 30 minutes prior to chemotherapy, followed by the same dose 7.5 hours following chemotherapy. Patients were also randomized to received either [metoclopramide](#) 2 mg/kg IV (30 minutes prior to chemotherapy and at 1.5, 3.5 and 7.5 hours after chemotherapy) or [prochlorperazine](#) 12.5 mg at 30 minutes before chemotherapy and 3.5 and 7.5 hours after chemotherapy. The [metoclopramide/lorazepam](#) regimen significantly reduced the severity of vomiting, duration of vomiting and number of vomiting episodes as compared with [prochlorperazine/lorazepam](#). It is suggested that the [metoclopramide/lorazepam](#) regimen is preferred if vomiting is distressing, especially in patients receiving cisplatin.

#### 4.6.AB] [Midazolam](#)

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

**a)** [Midazolam](#) 15 milligrams (mg) was significantly superior to [lorazepam](#) 1 mg in decreasing sleep latency and increasing duration of sleep in 82 insomniacs. Pairs of patients were treated with either [midazolam](#) or [lorazepam](#) and the results were compared. [Midazolam](#) was superior to [lorazepam](#) in terms of number of awakenings and evaluation by the patients; this difference was not statistically significant [358].

##### 4.6.AB.2] [Sedation](#)

**a)** [Midazolam](#) and [lorazepam](#) were equally efficacious when used for sedation in the intensive care unit in an 8-hour, multicenter study, but [lorazepam](#) was more cost efficient (Cernaianu et al, 1996). [Midazolam](#) was given as a bolus injection and continuous infusion in 45 patients, and [lorazepam](#) was given intermittently in 50 patients. There were no significant differences between the 2 groups in quality of anxiolysis or sedation, hemodynamic or oxygen-transport variables, or side effects. The only significant difference was that approximately 1.6 milligrams (mg) of [lorazepam](#) and 14.4 mg of [midazolam](#) were used during the 8-hour study period ( $p=0.001$ ). [Midazolam](#) has a faster systemic elimination and lower potency than [lorazepam](#), which explains the higher total dose requirements. The generic cost to the hospitals at the time of the study was \$1.85/mg for [lorazepam](#) and \$1.73/mg for [midazolam](#). Because of equal efficacy and safety in the critically ill patient, cost efficiency makes [lorazepam](#) the preferred drug in this setting.

**b)** After comparing the efficacy of continuous infusions of [LORAZEPAM](#) and [MIDAZOLAM](#) for sedation in a group of 20 intensive care unit patients, one study questions whether this mechanism of delivery is optimal to sedate critically ill patients. Findings in the study included a longer than desired time required to achieve adequate sedation (124 minutes for [LORAZEPAM](#) and 105 minutes for [MIDAZOLAM](#)). Doses required to maintain sedation were larger than current literature describes (maximum and mean infusion rates were 0.1 and 0.06 milligram/kilogram/hour (mg/kg/hr), respectively, for [lorazepam](#) and 0.29 and 0.24 mg/kg/hr, respectively, for [midazolam](#)). Time to return to baseline mental status after discontinuation of the infusion was occasionally delayed for greater than 24 hours (all patients

in the lorazepam group returned to baseline in less than 12 hours). Large fluid volumes were required to deliver drug dosages (mean daily fluid volume required to deliver the maximum dose was approximately 1.2 L for lorazepam and 1.3 L for midazolam). Costs of this method of benzodiazepine delivery may be greater than \$1,000/day (Pohlman, 1994).

c) Lorazepam, midazolam, and propofol were shown to be efficacious for sedation in critically ill trauma and surgery patients, but lorazepam was more cost effective. In a prospective, randomized, nonblinded study conducted in a single center, 30 mechanically ventilated patients were given lorazepam (0.05 milligram (mg)/kilogram (kg) bolus followed by 0.007 mg/kg/hour continuous infusion), midazolam (0.05 mg/kg bolus followed by 0.003 mg/kg/hour continuous infusion), or propofol (0.25 mg/kg bolus followed by 0.06 mg/kg/hour continuous infusion) and followed for 10 days or until sedation was no longer required. Once adequate sedation was attained, agents were titrated to maintain the desired response. The maintenance doses were 0.02 +/- 0.01 mg/kg/hr for lorazepam, 0.04 +/- 0.03 mg/kg/hr for midazolam and 2 +/- 1.5 mg/kg/hr for propofol. The duration of sedation was not significantly different between the 3 groups (mean duration of sedation=3 days). Sedation was assessed with the Modified Ramsay Sedation Scale and doses were manipulated to achieve scores greater than or equal to 2 or less than 5. Adequate sedation occurred in 79% of midazolam patients compared to 68% of lorazepam patients (p=0.03) and 62% of propofol patients (p=0.24). Oversedation occurred in 14% of lorazepam patients compared to 6% of midazolam patients (p=0.03) and 7% of propofol patients (p=0.02) which is potentially due the longer duration of effect following lorazepam administration. In the midazolam group, 2 patients discontinued treatment because they became unresponsive to the drug and 1 patient experienced transient hypotension. In the propofol group, 2 patients experienced transient hypotension and 1 patient developed a rash. Eighteen percent of lorazepam doses were discarded due to precipitation; however, the daily sedation cost of lorazepam remained significantly (p=0.005) less than midazolam (48 dollars +/- 76 versus 182 dollars +/- 98, respectively) [359].

#### 4.6.AC] Olanzapine

##### 4.6.AC.1] Agitation - Bipolar disorder

a) According to a randomized, double-blind study among 201 adults with manic or mixed bipolar disorder, agitation was significantly decreased 2 hours following intramuscular (IM) administration of olanzapine as measured by a significantly greater mean improvement in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) compared with lorazepam and with placebo. Adults included in the study (mean age of 40 +/- 11.3 years) had DSM-IV diagnosed bipolar disorder (minimum total score of 14 and at least 1 individual item score of at least 4 on the PANSS-EC at baseline) with severe agitation requiring treatment. Patients were randomized to receive IM injections of either olanzapine 10 milligrams (mg) IM for 2 doses, then 5 mg IM for a third dose (n=99), lorazepam 2 mg IM for 2 doses, then 1 mg IM for a third dose (n=51), or placebo for 2 doses, then olanzapine 10 mg IM for a third dose (n=51) within a 24-hour period. In all patients the optional second dose could be administered at least 2 hours following the first dose, and the optional third dose could be administered within 20 hours of the first dose. Static doses of lithium or valproate were permitted, as well as concomitant benztropine, biperiden, or procyclidine for the control of extrapyramidal symptoms. A response rate was defined as a reduction of at least 40% on the PANSS-EC at 2 hours following the first injection compared with baseline. In an intent-to-treat analysis, the mean change in PANSS-EC from baseline to 2 hours following the first dose was significantly improved in olanzapine-treated patients (-9.6 +/- 4.74) compared with lorazepam (-6.75 +/- 5.2; p=0.001), and with placebo (-4.84 +/- 4.66; p less than 0.001). Olanzapine-treated patients experienced significantly greater improvements in the PANSS-EC at time points 30 minutes (p=0.004), and at 60, 90, and 120 minutes (p less than 0.001 for each time period) compared with lorazepam and placebo groups. The response rate was 80.6% in olanzapine-treated patients compared with 64.7% (p=0.045) in lorazepam-treated patients, and 44% (p less than 0.001) in placebo. For the first 2 hours following injection, olanzapine

had significantly greater improvements on 2 additional agitation scales including the Agitated Behavior Scale (ABS) (-11.3 +/- 6.09) compared with lorazepam (-8.39 +/- 6.32;  $p=0.006$ ) and with placebo (-4.78 +/- 5.49;  $p$  less than 0.001) and on the Agitation-Calmness Evaluation Scale (ACES) (2.9 +/- 1.8) compared with lorazepam (1.88 +/- 1.77;  $p$  less than 0.001) and with placebo (0.82 +/- 1.4;  $p=0.001$ ). Although the benefits of olanzapine appeared to be statistically superior to placebo at 24 hours after the first injection, the difference between olanzapine and lorazepam did not reach statistical or clinical significance. Optional second or third injections were administered in 26.3% of olanzapine-treated patients compared with 52.9% ( $p=0.002$ ) of lorazepam-treated patients and 52.9% ( $p$  less than 0.001) in placebo. There were no significant differences between treatment groups in the incidence of treatment-emergent parkinsonism, akathisia, or QTc interval changes. However, olanzapine was associated with significant increase in orthostatic pulse rate (6.93 beats per minute (bpm)) compared with lorazepam (0.96 bpm) and placebo 0.35 bpm ( $p$  less than 0.009). Patients were required to sign an informed consent form for inclusion in the study and therefore the most severely agitated patients may not have been included [302].

#### 4.6.AD] Opium

##### 4.6.AD.1] Administration of medication - Preoperative care

a) Opium produced insignificant anxiety-reduction, less amnesia, and more nausea, vomiting, and headaches compared to lorazepam given as premedication for uterine curettage [352].

#### 4.6.AE] Oxazepam

##### 4.6.AE.1] Administration of medication - Preoperative care

a) Oxazepam was as effective as clobazam or diazepam and more effective than lorazepam for premedication prior to gynecological surgery. In a randomized, double-blind, placebo-controlled study, 150 patients received either clobazam 20 mg, diazepam 10 mg, lorazepam 2 mg, or oxazepam 30 mg. Diazepam induced the most drowsiness 1 hour after dosing and lorazepam caused more drowsiness and impaired psychomotor function than all the other agents at 2 and 4 hours after the procedure [304].

##### 4.6.AE.2] Chemotherapy-induced nausea and vomiting

a) Lorazepam was more effective in reducing nausea and vomiting in patients receiving cisplatin-containing chemotherapy than oxazepam or methylprednisolone. Eighty-five patients completed at least 2 of 3 consecutive chemotherapy regimens containing the same dose of cisplatin each time. Patients received single doses of lorazepam 2.5 milligrams/square meter, oxazepam 60 milligrams, and intravenous methylprednisolone 500 mg/hour prior to chemotherapy on 3 separate occasions. Lorazepam reduced the incidence of vomiting and caused more effective amnesia than either oxazepam or methylprednisolone. Oxazepam, however, was preferred for premedication over methylprednisolone by more patients [303].

#### 4.6.AF] Phenobarbital

##### 4.6.AF.1] Status epilepticus

a) Lorazepam was easier to use but no more effective than phenobarbital, or diazepam followed by phenytoin as initial therapy for status epilepticus (overt or subtle) [346]. In a multi-center, blinded study, patients were randomized to receive either lorazepam 0.1 milligrams/kilogram (mg/kg) ( $n=136$ ), phenytoin 18 mg/kg ( $n=127$ ), phenobarbital 15 mg/kg ( $n=124$ ), or diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg ( $n=131$ ). Patients were classified as having either overt generalized status epilepticus or subtle generalized convulsive status epilepticus. There was a significant difference in the frequency of success among the 4 treatments in those being treated for overt status epilepticus ( $p=0.02$ ), but no differences in



those treated for subtle [status epilepticus](#) ( $p=0.18$ ). The 4 groups were actually not significantly different when an intention to treat analysis was used. Combining the 2 groups, [lorazepam](#) was successful as first-line treatment in 52.2%, [phenobarbital](#) in 49.2%, [diazepam/phenytoin](#) in 43.1%, and [phenytoin](#) alone in 36.8%. [Lorazepam](#) was effective significantly more often than [phenytoin](#) ( $p=0.001$ ). [Lorazepam](#) also required the least time to infuse ( $p$  less than 0.001 in paired comparisons), and [phenytoin](#) took the longest ( $p$  less than 0.001).

#### 4.6.AG] [Phenytoin](#)

##### 4.6.AG.1] [Status epilepticus](#)

a) [Lorazepam](#) was easier to use but no more effective than [phenobarbital](#), or [diazepam](#) followed by [phenytoin](#) as initial therapy for [status epilepticus](#) (overt or subtle) [307]. In a multi-center, blinded study, patients were randomized to receive either [lorazepam](#) 0.1 milligrams/kilogram (mg/kg) ( $n=136$ ), [phenytoin](#) 18 mg/kg ( $n=127$ ), [phenobarbital](#) 15 mg/kg ( $n=124$ ), or [diazepam](#) 0.15 mg/kg followed by [phenytoin](#) 18 mg/kg ( $n=131$ ). Patients were classified as having either overt [generalized status epilepticus](#) or subtle [generalized convulsive status epilepticus](#). There was a significant difference in the frequency of success among the 4 treatments in those being treated for overt [status epilepticus](#) ( $p=0.02$ ), but no differences in those treated for subtle [status epilepticus](#) ( $p=0.18$ ). The 4 groups were actually not significantly different when an intention to treat analysis was used. Combining the 2 groups, [lorazepam](#) was successful as first-line treatment in 52.2%, [phenobarbital](#) in 49.2%, [diazepam/phenytoin](#) in 43.1%, and [phenytoin](#) alone in 36.8%. [Lorazepam](#) was effective significantly more often than [phenytoin](#) ( $p=0.001$ ). [Lorazepam](#) also required the least time to infuse ( $p$  less than 0.001 in paired comparisons), and [phenytoin](#) took the longest ( $p$  less than 0.001).

#### 4.6.AH] [Pregabalin](#)

##### 4.6.AH.1] [Generalized anxiety disorder](#)

a) In a manufacturer-sponsored, double-blinded, randomized, placebo-controlled trial, [pregabalin](#) and [lorazepam](#) were more effective than placebo in the treatment of [generalized anxiety disorder](#). Patients ( $n=276$ ) were randomized to 1 of 4 treatment arms: [pregabalin](#) 150 milligrams per day (mg/d), [pregabalin](#) 600 mg/d, [lorazepam](#) 6 mg/d or placebo. The study consisted of a 1-week placebo lead-in phase, a 4-week treatment phase and a 1-week taper. Each treatment arm showed a decrease in the total Hamilton Anxiety Scale (HAM-A) score from baseline. However, the decrease was significantly greater in the [pregabalin](#) 150 mg/d ( $p=0.03$ ), [pregabalin](#) 600 mg/d ( $p=0.003$ ) and [lorazepam](#) arms (0.0001) compared with placebo. [Pregabalin](#) 600 mg/d and [lorazepam](#) also showed a significant decrease in the HAM-A psychic subscale compared with placebo ( $p=0.008$ ,  $p=0.001$ ). [Pregabalin](#) 150 mg/d showed a decrease but this decrease did not reach statistical significance ( $p=0.09$ ). Dizziness (30.9%) was the most frequently reported adverse effect associated with [pregabalin](#) use. In the [lorazepam](#) group, somnolence (54.4%) was the most frequently occurring adverse effect. Of note, [pregabalin](#) was associated with a mean weight gain of 1.3 kilograms (kg) with the 150 mg/d dose and 2.2 kg with the 600 mg/d dose. [Lorazepam](#) was associated with a mean weight loss of 0.2 kg. [Lorazepam](#) was also associated with more withdrawal symptoms after 4 weeks of treatment ( $p=0.002$ ) [341].

b) [Pregabalin](#) 600 milligrams (mg) daily was compared to [lorazepam](#) 6 mg daily for treatment of [generalized anxiety disorder](#) in three manufacturer-supported, placebo-controlled studies. However, the comparative efficacy of these agents is unclear. Although both [pregabalin](#) and [lorazepam](#) were superior to placebo with regard to symptom reduction (Hamilton Anxiety Rating Scale (HAM-A)) in two of these studies, efficacy/statistical differences between these agents were not provided [342][343]. In a further study of similar design, there was no difference between treatment and placebo groups with respect to symptom reduction [342].

#### 4.6.AI] Prochlorperazine

##### 4.6.AI.1] Chemotherapy-induced nausea and vomiting

a) There were no significant differences in the efficacy of [prochlorperazine](#) compared to [lorazepam](#) in antiemetic regimens in [chemotherapy-induced nausea and vomiting](#) in a double-blind, cross-over study in 24 patients [357]. Intravenous [prochlorperazine](#) 20 mg or [lorazepam](#) 2 mg were added to a dexamethasone-diphenhydramine-thiethylperazine regimen. In 48 total cycles of treatment, nausea and vomiting were completely controlled in 54% of patients. Nine patients had a complete response with either drug, 5 patients with [lorazepam](#) only, and 2 patients with [prochlorperazine](#) only. Self-reported total symptom distress scores, particularly relating to fatigue and pain, were significantly better with [lorazepam](#) than [prochlorperazine](#) as measured by the Adapted Symptom Distress Scale.

#### 4.6.AJ] Propofol

##### 4.6.AJ.1] Sedation

a) [Propofol](#) infusions with daily interruption of sedation resulted in significantly fewer ventilator days compared with intermittent bolus dosing of [lorazepam](#) in ICU patients requiring more than 48 hours of mechanical ventilation, according to a randomized, open-label trial conducted at 2 medical centers and involving 132 adults. Subjects were included based on an anticipated need of ventilator support exceeding 48 hours (based on respiratory strength and gas exchange during the first 24 hr) and a requirement of 6 or more doses or a total of 10 mg of [lorazepam](#) within 24 hr, or in the judgement of the primary ICU team, requirement of continuous sedation due to agitation or ventilator asynchrony. Relevant exclusion criteria included [benzodiazepine dependence](#), high risk of alcohol withdrawal, history of [pancreatitis](#) or evidence of active [pancreatitis](#), resuscitation from [cardiac arrest](#) without recovery of mental status, transfer from an outside institution where the patient had already received sedative for more than 24 hr, [head trauma](#) or acute neurologic injury with Glasgow Coma Score higher than 8, or death was expected within 24 hr. Patients randomly assigned to the intermittent bolus [lorazepam](#) group were given [lorazepam](#) 2 mg to 4 mg IV every 4 hours, with additional doses of 2 mg to 4 mg allowed per the bedside nurse. Patients randomly assigned to the daily interruption [propofol](#) group were started on an infusion of 5 mcg/kg/min, which was increased every 10 min as needed to a maximum of 80 mcg/kg/min. Treatment was titrated in both groups to a target Ramsay score of 2 to 3. Patient arousal was assessed at least every 2 hours and medication adjusted to maintain the target Ramsay score. Opiate pain relief was used to ensure adequate pain control. [Lorazepam](#) or [propofol](#) infusions were stopped each morning to allow patient awakening and to assess neurologic function. Sedation was held as long as patients remained comfortable. [Weaning from the ventilator](#) using spontaneous breathing trials (SBT) was evaluated by standard practice at both institutions in all study patients. On average, patients were enrolled 1.5 days after intubation. Patients in the [lorazepam](#) group received a median of 11.5 mg per ventilator day. Patients in the [propofol](#) group received a mean of 24.4 mcg/kg/min. Median ventilator days in the [propofol](#) group was 5.8 compared to 8.4 in the [lorazepam](#) group ( $p=0.04$ ), and is attributed to the difference between groups for hospital survivors (4.4 days in the [propofol](#) group compared to 9 days in the [lorazepam](#) group;  $p=0.006$ ). There was no difference in median ventilator days between groups for nonsurvivors (7.2 compared to 7.5, respectively,  $p=0.66$ ). The secondary outcome of median 28-day ventilator-free survival was 18.5 days in the [propofol](#) group and 10.2 days in the [lorazepam](#) group ( $p=0.06$ ). Patients in the [propofol](#) group spent 8.3 days in the ICU compared to 10.4 days for the [lorazepam](#) group ( $p=0.2$ ), but for hospital survivors, ICU length of stay was shorter for the [propofol](#) group (8.6 days compared to 12.5 days,  $p=0.05$ ). The median hospital length of stay was not significantly different (18 days in the [lorazepam](#) group and 20 days in the [propofol](#) group, and hospital mortality was 25% and 24%, respectively ( $p=0.82$ ) [288].



b) Lorazepam, midazolam, and propofol were shown to be efficacious for sedation in critically ill trauma and surgery patients, but lorazepam was more cost effective. In a prospective, randomized, nonblinded study conducted in a single center, 30 mechanically ventilated patients were given lorazepam (0.05 milligram (mg)/kilogram (kg) bolus followed by 0.007 mg/kg/hour continuous infusion), midazolam (0.05 mg/kg bolus followed by 0.003 mg/kg/hour continuous infusion), or propofol (0.25 mg/kg bolus followed by 0.06 mg/kg/hour continuous infusion) and followed for 10 days or until sedation was no longer required. Once adequate sedation was attained, agents were titrated to maintain the desired response. The maintenance doses were 0.02 +/- 0.01 mg/kg/hour for lorazepam, 0.04 +/- 0.03 mg/kg/hour for midazolam and 2 +/- 1.5 mg/kg/hour for propofol. The duration of sedation was not significantly different between the 3 groups (mean duration of sedation=3 days). Sedation was assessed with the Modified Ramsay Sedation Scale and doses were manipulated to achieve scores greater than or equal to 2 or less than 5. Adequate sedation occurred in 79% of midazolam patients compared to 68% of lorazepam patients (p=0.03) and 62% of propofol patients (p=0.24). Oversedation occurred in 14% of lorazepam patients compared to 6% of midazolam patients (p=0.03) and 7% of propofol patients (p=0.02) which is potentially due the longer duration of effect following lorazepam administration. In the midazolam group, 2 patients discontinued treatment because they became unresponsive to the drug and 1 patient experienced transient hypotension. In the propofol group, 2 patients experienced transient hypotension and 1 patient developed a rash. Eighteen percent of lorazepam doses were discarded due to precipitation; however, the daily sedation cost of lorazepam remained significantly (p=0.005) less than midazolam (48 dollars +/- 76 versus 182 dollars +/- 98, respectively) [289].

#### 4.6.AK] Temazepam

##### 4.6.AK.1] Anxiety

a) All drugs were equally efficacious in relieving anxiety and depression in a study involving 51 psychiatric outpatients comparing lorazepam 2 milligrams with temazepam 20 milligrams and placebo. Lorazepam-treated patients had more side effects than placebo-treated patients [290].

##### 4.6.AK.2] Insomnia

a) Lorazepam 2 milligrams, oxazepam 30 milligrams, and temazepam 20 milligrams were equally efficacious in maintaining sleep in 20 psychogeriatric inpatients. Three patients experienced prolonged insomnia induced by the withdrawal of lorazepam. Lorazepam-treated patients had muscle relaxant effects after awakening [291].

b) Temazepam is as effective as lorazepam for treating sleep disturbance disorders. One hundred eighty-five patients randomly received temazepam 20 milligrams, lorazepam 1 milligrams, or placebo in a multicenter, single-blind study. Both active agents were significantly better than placebo for inducing sleep, but no difference was observed between lorazepam and temazepam [292].

#### 4.6.AL] Triazolam

##### 1) Adverse Effects

a) Triazolam and lorazepam disrupted psychomotor performance and learning to a comparable degree and also caused a like degree of sedation when given in equivalent doses. Triazolam (0.125, 0.25, 0.5, and 0.75 milligram (mg)/70 kilogram (kg)) and lorazepam (0, 1, 2, 4 and 6 mg/70 kg) were compared in eight healthy men using a double-blind, crossover design. The authors concluded that triazolam does not produce greater behavioral impairment than other commonly used benzodiazepines [356].

#### 4.6.AM] Trimeprazine

**4.6.AM.1] Administration of medication - Preoperative care**

a) **Lorazepam** 0.05 mg/kg PO offered no advantage over **trimeprazine** 3 mg/kg PO as a premedicant prior to ENT surgery in children [353].

b) **Lorazepam** 0.05 mg/kg and **trimeprazine** 3 mg/kg were compared as oral premedicants in 199 children undergoing ear, nose and throat surgery. While **lorazepam** was more palatable, no differences in efficacy were noted prior to surgery. Restlessness and vomiting were reported more frequently postoperatively in the lorazepam-treated group; **retrograde amnesia** was also more common. Three children who received **lorazepam** experienced hallucinations [353].

c) Placebo, **lorazepam** 0.05 mg/kg, **diazepam** 0.25 mg/kg, and **trimeprazine** 2.5 mg/kg were compared as premedication in 100 children undergoing surgical procedures [354]. All drugs were considered satisfactory premedicants, but **lorazepam** produced better amnesia than other drugs. No untoward side effects or cardiorespiratory depression were noted in any group.

**4.6.AN] Tropisetron****4.6.AN.1] Chemotherapy-induced nausea and vomiting**

a) Tropisetron monotherapy has been more effective than a combination regimen of **metoclopramide** plus **lorazepam** in the prevention of acute nausea and vomiting related to carboplatin-based chemotherapy in one randomized study [293] and cisplatin-based chemotherapy in another [294]. Delayed nausea and vomiting (on the first day after cisplatin chemotherapy) was also controlled more effectively with tropisetron; no significant difference between tropisetron and **metoclopramide/lorazepam** was evident on the second day following cisplatin [294]. Data regarding delayed nausea and vomiting after the carboplatin-containing regimen were not presented [293].

b) Tropisetron offers other advantages over **metoclopramide** combinations as it has minimal to no propensity to induce extrapyramidal reactions and is easier to administer. However, other serotonin-3-receptor antagonists (eg, **granisetron**) share these advantages, and the ultimate place in therapy of tropisetron will depend upon comparative studies with these agents.

**4.6.AO] Zaleplon****4.6.AO.1] Impaired psychomotor performance**

a) In healthy subjects, **zaleplon** 20 mg was associated with a lesser degree of **psychomotor impairment** and impaired memory than **lorazepam** 2 mg. Recovery of normal functioning was more rapid in the **zaleplon** group (3 versus 5 hours) [295]. However, **lorazepam** has a significantly longer half-life (14 hours) than **zaleplon**, and its longer duration of action is to be expected.

**6.0] References**

- 1 Mayo-Smith MF: Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 1997; 278(2):144-151. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 2 Product Information: lorazepam oral tablets, lorazepam oral tablets. Watson Laboratories, Inc., Corona, CA, 2008.
- 3 Product Information: lorazepam concentrated oral solution, lorazepam concentrated oral solution. Paddock Laboratories, Inc., Minneapolis, MN, 2008.

- 4 Pande A, Crockatt J, Feltner D, et al: Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; 160:533-540.
- 5 AMA Department of Drugs: Drug Evaluation Subscription, American Medical Association, Chicago, IL, 1991.
- 6 Ameer B & Greenblatt DJ: Lorazepam: a review of its clinical pharmacological properties and therapeutic uses. *Drugs* 1981; 21:161-200.
- 7 de Figueiredo R, Franchini A, Martinho A, et al: Differences in the effect of two benzodiazepines in the treatment of anxious outpatients. *Int Pharmacopsychiatr* 1981; 16:57-65.
- 8 Daniel JT & Zung WWK: A double-blind clinical comparison of prazepam, lorazepam, diazepam and placebo in the treatment of anxiety in a private surgical out-patient practice. *Curr Ther Res* 1981; 20:417-426.
- 9 Bonnet MH & Arand DL: The use of lorazepam TID for chronic insomnia. *Int Clin Psychopharmacol* 1999; 14:81-89.
- 10 Walsh JK, Schweitzer PK, & Parwatikar S: Effects of lorazepam and its withdrawal on sleep, performance, and subjective state. *Clin Pharmacol Ther* 1983; 34:496-500.
- 11 Scharf MB & Jacoby JA: Lorazepam--efficacy, side effects, and rebound phenomena. *Clin Pharmacol Ther* 1982; 31:175-179.
- 12 Product Information: lorazepam IM, IV injection, lorazepam IM, IV injection. Akorn, Inc, Lake Forest, IL, 2008.
- 13 Maltais F, Laberge F, & Laviolette M: A randomized, double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. *Chest* 1996; 109:1195-1198.
- 14 Russell WJ: Lorazepam as a premedicant for regional anaesthesia. *Anaesthesia* 1983; 38:1062-1065.
- 15 Ghanchi FD & Khan MY: Sublingual lorazepam as premedication in peribulbar anesthesia. *J Cataract Refract Surg* 1997; 23:1581-1584.
- 16 Barclay JK, Hunter KMac D, & Jones H: Diazepam and lorazepam compared as sedatives for outpatient third molar surgery. *Br J Oral Surg* 1980; 18:141-149.
- 17 Rubin J, Schwegmann I, & Uys P: Lorazepam as a premedicant in dental surgery. *S Afr Med J* 1980; 29:124-126.
- 18 Wilson J & Ellis FR: Oral premedication with lorazepam (Ativan(R)): a comparison with heptabarbitalone (Medomin(R)) and diazepam (Valium(R)). *Br J Anaesth* 1973; 45:738-744.
- 19 McAuley DM, O'Neill MP, Moore J, et al: Lorazepam premedication for labour. *Br J Obstet Gynaecol* 1982; 89:149-154.
- 20 Studd C & Eltringham RJ: Lorazepam as night sedation and premedication: a comparison with diazepam. *Anaesthesia* 1980; 35:60-64.
- 21 Saccomanno PM, Kavanagh BP, Cheng DCH, et al: comparison of lorazepam alone vs lorazepam, morphine, and perphenazine for cardiac premedication. *Can J Anaesth* 1997; 44:146-153.
- 22 Burtles R & Astley B: Lorazepam in children: a double-blind trial comparing lorazepam, diazepam, trimeprazine and placebo. *Br J Anaesth* 1983; 55:275-279.
- 23 Cornejo G, Araneda LB, & Gallardo F: Use of lorazepam as premedication for apprehensive children. *J Pedodont* 1985; 9:136-141.
- 24 Hardman JG, Gilman AG, & Limbird LE (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th. McGraw-Hill, New York, NY, 1996.
- 25 Korttila K, Levanen J, & Auvonen J: Failure of intramuscularly administered lorazepam and scopolamine-morphine premedication to produce amnesic effects to supplement conduction anesthesia. *Acta Anaesth Scand* 1980; 24:325-330.

- 26 Friedlander ML, Kearsley JH, Sims K, et al: Lorazepam as an adjunct to antiemetic therapy with haloperidol in patients receiving cytotoxic chemotherapy. *Aust N Z J Med* 1983; 13:53-56.
- 27 Friedlander ML, Kearsley JH, & Tattersall MHN: Oral lorazepam to improve tolerance of cytotoxic therapy. *Lancet* 1981; 1(8233):1316-1317.
- 28 Maher J: Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy. *Lancet* 1981; 1:91-92.
- 29 Roila F, Basurto C, Baracorda M, et al: A pilot study of metoclopramide, dexamethasone, diphenhydramine, and lorazepam in prevention of nausea and vomiting in cisplatin-treated male patients. *Oncology* 1990; 47:415-417.
- 30 van Hoff J & Olszewski D: Lorazepam for the control of chemotherapy-related nausea and vomiting in children. *J Pediatr* 1988; 113:146-149.
- 31 Treiman DM, Meyers PD, Walton NY, et al: A comparison of four treatments for generalized convulsive status epilepticus. *N Eng J Med* 1998; 339(12):792-798.
- 32 Vincent FM & Vincent T: Lorazepam in myoclonic seizures after cardiac arrest. *Ann Intern Med* 1986; 104:586.
- 33 Leppik IE, Derivan AT, Homan RW, et al: Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; 249:1452-1454.
- 34 Walker JE, Homan RW, Vasko MR, et al: Lorazepam in status epilepticus. *Ann Neurol* 1979; 6:207-213.
- 35 Crawford TO, Mitchell WG, & Snodgrass S: Lorazepam in childhood status epilepticus and serial seizures: effectiveness and tachyphylaxis. *Neurology* 1987; 37:190-195.
- 36 Lacey DJ, Singer WD, Horwitz SJ, et al: Clinical and laboratory observations: lorazepam therapy of status epilepticus in children and adolescents. *J Pediatr* 1986; 108:771-774.
- 37 Goldbloom AL: The use of lorazepam in the management of seizures. *Pediatr Rev* 1990; 12:31.
- 38 Patterson DR, Ptacek JT, Carrougner GJ, et al: Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. *Pain* 1997; 72:367-374.
- 39 Bieniek SA, Ownby RL, Penalver A, et al: A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; 18:57-62.
- 40 Battaglia J, Moss S, Rush J, et al: Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; 15:335-340.
- 41 Jacobi J, Fraser GL, Coursin DB, et al: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30(1):119-141. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 42 Shapiro BA, Warren J, Egol AB, et al: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Crit Care Med* 1995; 23:1596-1600.
- 43 Simpson PJ & Eltringham RJ: Lorazepam in intensive care. *Clin Ther* 1981; 4:150-163.
- 44 D'Onfrio G, Rathlev NK, Ulrich AS, et al: Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; 340(12):915-919.
- 45 Walker JE, Homan RW, & Crawford IL: Lorazepam: a controlled trial in patients with intractable partial complex seizures. *Epilepsia* 1984; 25:464-466.
- 46 Yager JY & Seshia SS: Sublingual lorazepam in childhood serial seizures. *Am J Dis Child* 1988; 142:931-932.
- 47 Roddy SM, McBride MC, & Torres CF: Treatment of neonatal seizures with lorazepam (abstract). *Ann Neurol* 1987; 22:412.

- 48 Deshmukh A, Wittert W, Schnitzler E, et al: Lorazepam in the treatment of refractory neonatal seizures: a pilot study. *Am J Dis Child* 1986; 140:1042-1044.
- 49 Chan KW, Mullen CA, Worth LL, et al: Lorazepam for seizure prophylaxis during high-dose busulfan administration. *Bone Marrow Transplantation* 2002; 29:963-965.
- 50 Verbeeck RK, Tjandramaga TB, De Schepper PH, et al: Impaired elimination of lorazepam following subchronic administration in two patients with renal failure. *Br J Clin Pharmacol* 1981; 12:749-752.
- 51 Bennett WM, Aronoff GR, Golper TA, et al: *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*, 3rd. American College of Physicians, Philadelphia, PA, 1994.
- 52 Greenblatt DJ: Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; 6:89-105.
- 53 Wilkinson G: The effects of liver disease and aging on the disposition of diazepam, chlordiazepoxide, oxazepam and lorazepam in man. *Acta Psychiatr Scand* 1978; 274(suppl):56-74.
- 54 Greenblatt D & Shader R: Pharmacokinetic understanding of antianxiety drug therapy. *South Med J* 1978; 71:2-9.
- 55 Kraus JW, Desmond PV, Marshall JP, et al: Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; 24:411-419.
- 56 Banen DM & Resnick O: Lorazepam versus glutethimide as a sleep-inducing agent for the geriatric patient. *J Am Geriatr Soc* 1973; 21:507.
- 57 Product Information: Ativan(R), lorazepam. Wyeth, Philadelphia, PA, 2002.
- 58 Aronoff GR, Bennett WM, Berns JS, et al: *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed.. American College of Physicians, Philadelphia, PA, 2007.
- 59 Abernethy DR, Greenblatt DJ, Divoll M, et al: Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. *J Lab Clin Med* 1983a; 101:873.
- 60 Segal JL & Brunneman SR: Clinical pharmacokinetics in patients with spinal cord injuries. *Clin Pharmacokinet* 1989; 17:109-129.
- 61 Product Information: ATIVAN(R) intramuscular, intravenous injection, lorazepam intramuscular, intravenous injection. Baxter Healthcare Corporation, Deerfield, IL, 2006.
- 62 Product Information: ATIVAN(R) oral tablets, lorazepam oral tablets. Biovail Pharmaceuticals, Inc, Bridgewater, NJ, 2007.
- 63 Product Information: ATIVAN(R) IM, IV injection, lorazepam IM, IV injection. Baxter Healthcare Corporation, Deerfield, IL, 2006.
- 64 Scharf MB & Jacoby JA: Lorazepam--efficacy, side effects, and rebound phenomena. *Clin Pharmacol Ther* 1982; 31:175-179.
- 65 Walsh JK, Schweitzer PK, & Parwatikar S: Effects of lorazepam and its withdrawal on sleep, performance, and subjective state. *Clin Pharmacol Ther* 1983; 34:496-500.
- 66 Sandyk R: Orofacial dyskinesias associated with lorazepam therapy. *Clin Pharm* 1986; 5:419-421.
- 67 Chess PR & D'Angio CT: Clonic movements following lorazepam administration in full-term infants. *Arch Pediatr Adolesc Med* 1998; 153:98-99.
- 68 DiMario FJ Jr & Clancy RR: Paradoxical precipitation of tonic seizures by lorazepam in a child with atypical absence seizures. *Pediatr Neurol* 1988; 4:249-251.
- 69 Roila F, Basurto C, Baracorda M, et al: A pilot study of metoclopramide, dexamethasone, diphenhydramine, and lorazepam in prevention of nausea and vomiting in cisplatin-treated male patients. *Oncology* 1990; 47:415-417.

- 70 Korttila K, Tarkkanen L, Kuurne, et al: Unpredictable central nervous system effects after lorazepam premedication for neurosurgery. *Acta Anaesth Scand* 1982; 26:213-216.
- 71 Elliott HW, Nomof N, Navarro G, et al: CNS and cardiovascular effects of lorazepam in man. *Clin Pharmacol Ther* 1971; 12:468-481.
- 72 Bell RW, Dickie DS, Stewart-Jones, et al: Lorazepam on visuo-motor co-ordination and visual function in man. *J Pharm Pharmacol* 1973; 25(1):87-88.
- 73 Scharf MB, Khosla N, Lysaght R, et al: Anterograde amnesia with oral lorazepam. *J Clin Psychiatry* 1983; 44:362-364.
- 74 Olgiati SG: Clinical assessment of lorazepam in anxiety: a double-blind study. *Curr Ther Res* 1975; 17:13.
- 75 Krueger GA: Use of lorazepam in treating patients with neurotic and somatized psychovegetative symptoms. *Curr Ther Res* 1973; 15(12):907-914.
- 76 Blitt CD & Petty WC: Reversal of lorazepam delirium by physostigmine. *Anesth Analg* 1975; 54:607.
- 77 Arroliga AC, Shehab N, McCarthy K, et al: Relationship of continuous infusion lorazepam to serum propylene glycol concentration in critically ill adults. *Crit Care Med* 2004; 32(8):1709-1714. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 78 Yaucher NE, Fish JT, Smith HW, et al: Propylene glycol-associated renal toxicity from lorazepam infusion. *Pharmacotherapy* 2003; 23(9):1094-1099.
- 79 Tayar J, Jabbour G, & Saggi SJ: Severe hyperosmolar metabolic acidosis due to a large dose of intravenous lorazepam (letter). *N Engl J Med* 2002; 346(16):1253.
- 80 Seay RS, Graves PJ, & Wilkin MK: Comment: possible toxicity from propylene glycol in lorazepam infusion (letter). *Ann Pharmacother* 1997; 31:647-648.
- 81 Briggs M & Briggs M: Pyrimethamine toxicity. *Br Med J* 1974; 1:40.
- 82 Dr Gail Corrado, Wyeth Laboratories
- 83 Jed Sudel, Roche Laboratories
- 84 Belfer ML: Psychotropic Drug Side Effects, Williams and Wilkens, Baltimore, MD, 1970, pp 116-123.
- 85 Pandharipande P, Shintani A, Peterson J, et al: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; 104(1):21-26. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 86 Product Information: ATIVAN(R) oral tablets, lorazepam oral tablets. Wyeth Pharmaceuticals Inc., Philadelphia, PA, 2007.
- 87 Fisman M: Musical hallucinations: report of two unusual cases. *Can J Psychiatry* 1991; 36:609-610.
- 88 Glover SG, Escalona R, Bishop J, et al: Catatonia associated with lorazepam withdrawal. *Psychosomatics* 1997; 38:148-150.
- 89 Busto U, Sellers EM, Naranjo CA, et al: Withdrawal reaction after long-term therapeutic use of benzodiazepines. *N Engl J Med* 1986; 315:854-859.
- 90 Griffiths RR & Wolf B: Relative abuse liability of different benzodiazepines in drug abusers. *J Clin Psychopharmacol* 1990; 10:237-243.
- 91 de la Fuente JR, Rosenbaum AH, Martin HR, et al: Lorazepam-related withdrawal seizures. *Mayo Clin Proc* 1980; 55:190-192.
- 92 Stewart RB, Salem RB, & Springer PK: A case report of lorazepam withdrawal. *Am J Psychiatry* 1980; 137:1113-1114.



- 93 Einarson TR: Lorazepam withdrawal seizures. *Lancet* 1980; 1:151.
- 94 Rigby J, Harvey M, & Davies DR: Mania precipitated by benzodiazepine withdrawal. *Acta Psychiatr Scand* 1989; 79:406-407.
- 95 Product Information: XENICAL(R) oral capsules, orlistat oral capsules. Genentech USA Inc. (per FDA), South San Francisco, CA, 2013.
- 96 Product Information: LUSEDRA(R) IV injection, fospropofol disodium IV injection. Eisai Corporation, Research Triangle Park, NC, 2008.
- 97 Product Information: Xyrem(R), sodium oxyburate oral solution. Orphan Medical, Inc., Minnetonka, MN, 2002.
- 98 Henauer SA, Hollister LE, Gillespie HK, et al: Theophylline antagonizes diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; 25:743-747.
- 99 Arvidsson S, Niemand D, Martinell S, et al: Aminophylline reversal of diazepam sedation. *Anaesthesia* 1984; 39:806-809.
- 100 Stirt JA: Aminophylline is a diazepam antagonist. *Anesth Analg* 1981; 60:767-768.
- 101 Meyer BH, Weis OF, & Muller FO: Antagonism of diazepam by aminophylline in healthy volunteers. *Anesth Analg* 1984; 63:900-902.
- 102 Wangler MA & Kilpatrick DS: Aminophylline is an antagonist of lorazepam. *Anesth Analg* 1985; 64:834-836.
- 103 Gallen JS: Aminophylline reversal of midazolam sedation (letter). *Anesth Analg* 1989; 69:268.
- 104 Gurel A, Elevli M, & Hamulu A: Aminophylline reversal of flunitrazepam sedation. *Anesth Analg* 1987; 66:333-336.
- 105 Sleight JW: Failure of aminophylline to antagonize midazolam sedation (letter). *Anesth Analg* 1986; 65:540.
- 106 Tuncok Y, Akpinar O, Guven H, et al: The effects of theophylline on serum alprazolam levels. *Int J Clin Pharmacol Ther* 1994; 32:642-645.
- 107 Stirt JA: Aminophylline is a diazepam antagonist. *Anesth Analg* 1981; 60:767-768.
- 108 Wangler MA & Kilpatrick DS: Aminophylline is an antagonist of lorazepam. *Anesth Analg* 1985; 64:834-836.
- 109 Gurel A, Elevli M, & Hamulu A: Aminophylline reversal of flunitrazepam sedation. *Anesth Analg* 1987; 66:333-336.
- 110 Gallen JS: Aminophylline reversal of midazolam sedation (letter). *Anesth Analg* 1989; 69:268.
- 111 Bonfiglio MF & Dasta JF: Clinical significance of the benzodiazepine-theophylline interaction. *Pharmacotherapy* 1991; 11:85-87.
- 112 Product Information: ROMAZICON(R) injection, flumazenil injection. Roche Laboratories, Inc, Nutley, NJ, 2007.
- 113 Kawaguchi A, Ohmori M, Tsuruoka S, et al: Drug interaction between St John's Wort and quazepam. *Br J Clin Pharmacol* 2004; 58(4):403-410. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 114 Dresser GK, Schwarz UI, Wilkinson GR, et al: Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* 2003; 73(1):41-50.
- 115 Wang Z, Gorski JC, Hamman MA, et al: The effects of St. John's Wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001; 70(4):317-326.
- 116 Markowitz JS, Donovan JL, DeVane CL, et al: Effect of St John's Wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003; 290(11):1500-1504.
- 117 Gurley BJ, Gardner SF, Hubbard MA, et al: Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin Pharmacol Ther* 2002; 72(3):276-287.



- 118 Product Information: DOLOPHINE(R) oral tablets, methadone HCl oral tablets. Roxane Laboratories, Inc. (per FDA), Columbus, OH, 2014.
- 119 Abernethy DR, Greenblatt DJ, Steel K, et al: Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; 97:223-224.
- 120 Abernethy DR, Greenblatt DJ, Steel K, et al: Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; 97:223-224.
- 121 Product Information: Demerol(R), meperidine hydrochloride. Sanofi-Synthelabo Inc., New York, NY, 2002.
- 122 Product Information: Versed(R), midazolam HCl injection. Roche Pharmaceuticals, Nutley, NJ, 2000.
- 123 Cobb CD, Anderson CB, & Seidel DR: Possible interaction between clozapine and lorazepam (letter). *Am J Psychiatry* 1991; 148:1606-1607.
- 124 Product Information: Clozaril(R), clozapine. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 1997.
- 125 Product Information: BUNAVAIL(TM) buccal film, buprenorphine naloxone buccal film. BioDelivery Sciences International (per FDA), Raleigh, North Carolina, 2014.
- 126 Product Information: REMERONSolTab(R) oral disintegrating tablets, mirtazapine oral disintegrating tablets. Merck Sharp & Dohme Corp. (per FDA), Whitehouse Station, NJ, 2014.
- 127 Birket-Smith E & Mikkelsen B: Preliminary observations on the effect of a new benzodiazepine (RO-5-4023) in epilepsy. *Acta Neurol Scand* 1972; 48(suppl):385-395.
- 128 Aarli J: Effect of clonazepam (RO5-4023) on epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):11.
- 129 Mikkelsen B & Birket-Smith E: A clinical study of the benzodiazepine RO5-4023 (clonazepam) in the treatment of epilepsy. *Acta Neurol Scand* 1973; 49(suppl 53):91-96.
- 130 Munthe-Kaas A: Clonazepam in the treatment of epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):97.
- 131 Hooshmond H: Trial of a new anticonvulsant for uncontrollable minor motor seizures. *Epilepsia* 1971; 12:277.
- 132 Tverskoy M, Fleyshman G, Bradley EL, et al: Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg* 1988; 67:342-345.
- 133 Short TG, Galletly DC, & Plummer JL: Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; 66:13-19.
- 134 Product Information: Versed(R), midazolam. Roche Laboratories Inc., Nutley, NJ, 2000.
- 135 Wilder-Smith OHG, Ravussin PA, Decosterd LA, et al: Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1999; 83:590-595.
- 136 Birket-Smith E & Mikkelsen B: Preliminary observations on the effect of a new benzodiazepine (RO-5-4023) in epilepsy. *Acta Neurol Scand* 1972; 48(suppl):385-395.
- 137 Aarli J: Effect of clonazepam (RO5-4023) on epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):11.
- 138 Mikkelsen B & Birket-Smith E: A clinical study of the benzodiazepine RO5-4023 (clonazepam) in the treatment of epilepsy. *Acta Neurol Scand* 1973; 49(suppl 53):91-96.
- 139 Munthe-Kaas A: Clonazepam in the treatment of epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):97.
- 140 Hooshmond H: Trial of a new anticonvulsant for uncontrollable minor motor seizures. *Epilepsia* 1971; 12:277.

- 141 Abernethy DR, Greenblatt DJ, Ameer B, et al: Probenecid impairment of acetaminophen and lorazepam clearance: direct inhibition of ether glucuronide formation. *J Pharmacol Exp Ther* 1985; 234:345-349.
- 142 Product Information: Ativan(R), lorazepam. Wyeth Laboratories Inc., Philadelphia, PA, 1997.
- 143 Product Information: BELSOMRA(R) oral tablets, suvorexant oral tablets. Merck Sharp & Dohme Corp. (per manufacturer), Whitehouse Station, NJ, 2014.
- 144 Carrasco MC, Vallejo JR, Pardo-de-Santayana M, et al: Interactions of *Valeriana officinalis* L. and *Passiflora incarnata* L. in a patient treated with lorazepam. *Phytother Res* 2009; 23(12):1795-1796. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/>... PubMed Article: <http://www.ncbi.nlm.nih.gov/>...
- 145 Holzl J & Godau P: Receptor binding studies with *Valeriana officinalis* on the benzodiazepine receptor. *Planta Med* 1989; 55:642.
- 146 Cavadas C, Araujo I, Cotrim MD, et al: In vitro study on the interaction of *Valeriana officinalis* L. extracts and their amino acids on GABA-A receptor in rat brain. *Arzneim-Forsch/Drug Res* 1995; 45(7):753-755.
- 147 Santos MS, Ferreira F, Faro C, et al: The amount of GABA present in aqueous extracts of valerian is sufficient to account for (3H)GABA release in synaptosomes. *Planta Med* 1994; 60(5):475-476.
- 148 Holzl J & Godau P: Receptor binding studies with *Valeriana officinalis* on the benzodiazepine receptor. *Planta Med* 1989; 55:642.
- 149 Kriegelstein VJ & Grusla D: Central dampfende Inhaltsstoffe im Baldrian: Valepotriate, Valeransaeure, Valeranon und atherisches Ol sind jedoch unwirksam. *Deutsche Apotheker Zeitung* 1988; 40:2041-2046.
- 150 Medina JH, Pena C, deStein ML, et al: Benzodiazepine-like molecules, as well as other ligands for the brain benzodiazepine receptors are relatively common constituents of plants. *Biochem Biophys Res Comm* 1989; 165:547-553.
- 151 Mennini T, Bernasconi P, Bombardelli F, et al: In vitro study on the interaction of extracts and pure compounds from *Valeriana officinalis* roots with GABA, benzodiazepine and barbiturate receptors in rat brain. *Fitoterapia* 1993; 64:291-300.
- 152 Mennini T, Bernasconi P, Bombardelli F, et al: In vitro study on the interaction of extracts and pure compounds from *Valeriana officinalis* roots with GABA, benzodiazepine and barbiturate receptors in rat brain. *Fitoterapia* 1993; 64:291-300.
- 153 Product Information: GATTEX(R) subcutaneous injection powder, teduglutide (rDNA origin) subcutaneous injection powder. Hospira, Inc. (per manufacturer), McPherson, KS, 2012.
- 154 Almeida JC & Grimsley EW: Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; 125:940-941.
- 155 Almeida JC & Grimsley EW: Coma from the health food store: interaction between kava and alprazolam (letter). *Ann Intern Med* 1996; 125:940-941.
- 156 Jussofie, SA, & Hiemke C: Kavapyrone enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. *Psychopharmacology (Berl)* 1994; 116:469-474.
- 157 Kuribara H, Stavinocha WB, & Maruyama Y: Behavioral pharmacological characteristics of honokiol, an anxiolytic agent present in extracts of magnolia bark, evaluated by an elevated plus-maze test in mice. *J Pharm Pharmacol* 1998; 50:819-826.
- 158 Tsai TH, Chou CJ, Cheng FC, et al: Pharmacokinetics of honokiol after intravenous administration in rats assessed using high-performance liquid chromatography. *J Chromatograph* 1994; 655(1):41-45.
- 159 Watanabe H, Watanabe K, & Hagino K: Chemostructural requirement for centrally acting muscle relaxant effect of magnolol and honokiol, neolignane derivatives. *J Pharm Dyn* 1983a; 6:184-190.

- 160 Watanabe K, Watanabe H, Goto Y, et al: Pharmacological properties of magnolol and honokiol extracted from *Magnolia officinalis*: central depressant effects. *Planta Med* 1983b; 49:103-108.
- 161 Watanabe H, Watanabe K, Goto Y, et al: Studies on the principles of *Magnolia* bark. Centrally acting muscle relaxant activity of magnolol and honokiol. *Jpn J Pharmacol* 1975; 25:605-607.
- 162 Watanabe H, Watanabe K, & Hagino K: Chemostructural requirement for centrally acting muscle relaxant effect of magnolol and honokiol, neolignane derivatives. *J Pharm Dyn* 1983a; 6:184-190.
- 163 Watanabe K, Watanabe H, Goto Y, et al: Pharmacological properties of magnolol and honokiol extracted from *Magnolia officinalis*: central depressant effects. *Planta Med* 1983b; 49:103-108.
- 164 Watanabe H, Watanabe K, Goto Y, et al: Studies on the principles of *Magnolia* bark. Centrally acting muscle relaxant activity of magnolol and honokiol. *Jpn J Pharmacol* 1975; 25:605-607.
- 165 Tsai TH, Chou CJ, Cheng FC, et al: Pharmacokinetics of honokiol after intravenous administration in rats assessed using high-performance liquid chromatography. *J Chromatograph* 1994; 655(1):41-45.
- 166 Kuribara H, Stavinoha WB, & Maruyama Y: Behavioral pharmacological characteristics of honokiol, an anxiolytic agent present in extracts of magnolia bark, evaluated by an elevated plus-maze test in mice. *J Pharm Pharmacol* 1998; 50:819-826.
- 167 Product Information: Karbinal(TM) ER oral extended-release suspension, carbinoxamine maleate oral extended-release suspension. Tris Pharma (per FDA), Monmouth Junction, NJ, 2013.
- 168 Product Information: carbinoxamine maleate oral tablets, oral syrup, carbinoxamine maleate oral tablets, oral syrup. Breckenridge Pharmaceutical, Inc. (per DailyMed), Boca Raton, FL, 2012.
- 169 Product Information: Ativan(R), lorazepam. Wyeth Laboratories Inc., Philadelphia, PA, 1997.
- 170 Anderson GD, Gidal BE, Kantor ED, et al: Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. *Epilepsia* 1994; 35:221-225.
- 171 Product Information: Ativan(R), lorazepam. Wyeth Laboratories Inc., Philadelphia, PA, 1997.
- 172 Product Information: ZYPREXA(R) IntraMuscular IM injection, olanzapine IM injection. Lilly USA, LLC (per manufacturer), Indianapolis, IN, 2011.
- 173 Medina JH, Paladini RC, Wolfman C, et al: Chrysin (5,7,-di-OH-flavone), a naturally-occurring ligand for benzodiazepine receptors with anticonvulsant properties. *Biochem Pharmacol* 1990; 40(10):2227-2231.
- 174 Speroni E, Billi R, Crespi Perellino N, et al: Role of chrysin in the sedative effects of *Passiflora incarnata* L. *Phytother Res* 1996; 10:S98-S100.
- 175 Gattuso S, Di Sapio O, McCargo J, et al: *Passiflora caerulea* (sic) and its adulterator *Cucurbitella asperata*. *Fitoterapia* 1996; 67(6):535-544.
- 176 Lee CM, Wong HCN, Chui KY, et al: Miltirone, a central benzodiazepine receptor partial agonist from a Chinese medicinal herb *Salvia miltiorrhiza*. *Neurosci Lett* 1991; 127:237-41.
- 177 Lee CM, Wong HCN, Chui KY, et al: Miltirone, a central benzodiazepine receptor partial agonist from a Chinese medicinal herb *Salvia miltiorrhiza*. *Neurosci Lett* 1991; 127:237-41.
- 178 Product Information: OxyContin(R) oral controlled-release tablets, oxycodone HCl oral controlled-release tablets. Purdue Pharma L.P. (per FDA), Stamford, CT, 2013.
- 179 Product Information: XARTEMIS(TM) XR oral extended-release tablets, oxycodone hydrochloride acetaminophen oral extended-release tablets. Mallinckrodt LLC (per manufacturer), Hazelwood, MO, 2014.

- 180 Product Information: NUCYNTA(TM) immediate-release oral tablets, tapentadol immediate-release oral tablets. PriCara, Raritan, NJ, 2009.
- 181 Product Information: ANTIVERT(R) oral tablets, meclizine HCl oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 182 Product Information: ANTIVERT(R)/25 oral tablets, meclizine HCl 25mg oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 183 Product Information: ANTIVERT(R)/50 oral tablets, meclizine HCl 50mg oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 184 Briggs M & Briggs M: Pyrimethamine toxicity. *BMJ* 1974; 1:40.
- 185 Product Information: Daraprim(R), pyrimethamine. GlaxoSmithKline, Research Triangle Park, NC, 2002.
- 186 Briggs M & Briggs M: Pyrimethamine toxicity. *BMJ* 1974; 1:40.
- 187 Patwardhan RV, Mitchell M, Johnson R, et al: Induction of glucuronidation by oral contraceptive steroids (abstract). *Clin Res* 1981; 29:861A.
- 188 Patwardhan RV, Mitchell MC, Johnson RF, et al: Differential effects of oral contraceptive steroids on the metabolism of benzodiazepines. *Hepatology* 1983; 3:248-253.
- 189 Product Information: Ativan(R), lorazepam. Wyeth Laboratories Inc., Philadelphia, PA, 1997.
- 190 Stoehr GP, Kroboth PD, Juhl RP, et al: Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; 36:683-690.
- 191 Abernethy DR, Greenblatt DJ, Ochs HR, et al: Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; 33:628-632.
- 192 Stoehr GP, Kroboth PD, Juhl RP, et al: Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; 36:683-690.
- 193 Abernethy DR, Greenblatt DJ, Ochs HR, et al: Lorazepam and oxazepam kinetics in women on low-dose oral contraceptives. *Clin Pharmacol Ther* 1983; 33:628-632.
- 194 Patwardhan RV, Mitchell M, Johnson R, et al: Induction of glucuronidation by oral contraceptive steroids (abstract). *Clin Res* 1981; 29:861A.
- 195 Product Information: Ativan(R), lorazepam. Wyeth Laboratories Inc., Philadelphia, PA, 1997.
- 196 Product Information: DURAGESIC(R) transdermal system, fentanyl transdermal system. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2012.
- 197 Hobbs W, Rall T, & Verdoorn T: Hypnotic sedatives - ethanol In: Hardman J & Limbird L (Eds): *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th. McGraw-Hill, New York, NY, 1996, pp 361-396.
- 198 Product Information: ADASUVE(TM) oral inhalation powder, loxapine oral inhalation powder. Alexza Pharmaceuticals, Inc. (per manufacturer), Mountain View, CA, 2012.
- 199 Product Information: loxapine oral capsules, loxapine oral capsules. Lannett Company, Inc. (per DailyMed), Philadelphia, PA, 2011.
- 200 Ishihara K, Kushida J, Yuzurihara M, et al: Interaction of drugs and Chinese herbs: pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J Pharm Pharmacol* 2000; 52(8):1023-1029.
- 201 Ishihara K, Kushida J, Yuzurihara M, et al: Interaction of drugs and Chinese herbs: pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J Pharm Pharmacol* 2000; 52(8):1023-1029.

- 202 Hui KM, Wang XH, & Xue H: Interaction of flavones from the roots of *Scutellaria baicalensis* with the benzodiazepine site. *Planta Med* 2000; 66(1):91-93.
- 203 Liao JF, Wang HH, Chen MC, et al: Benzodiazepine binding site-interactive flavones from *Scutellaria baicalensis* root. *Planta Med* 1998; 64(6):571-572.
- 204 Hui KM, Wang XH, & Xue H: Interaction of flavones from the roots of *Scutellaria baicalensis* with the benzodiazepine site. *Planta Med* 2000; 66(1):91-93.
- 205 Liao JF, Wang HH, Chen MC, et al: Benzodiazepine binding site-interactive flavones from *Scutellaria baicalensis* root. *Planta Med* 1998; 64(6):571-572.
- 206 Product Information: Placidyl(R), ethchlorvynol capsules. Abbott Laboratories, Abbott Park, IL, 1994.
- 207 Parfitt K (ed): *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press (Electronic version). Micromedex, Inc., Greenwood Village, CO, Edition expires 09/2002.
- 208 Product Information: Parafon Forte DSC(R), chlorzoxazone tablets. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2000.
- 209 Product Information: Dantrium(R), dantrolene sodium capsules. Procter and Gamble Pharmaceuticals, Cincinnati, OH, 1997.
- 210 Product Information: Soma(R), carisporodol tablets. Wallace Laboratories, Cranbury, NJ, 1994.
- 211 Product Information: FYCOMPA(TM) oral tablets, perampanel oral tablets. Eisai Inc. (per Manufacturer), Woodcliff Lake, NJ, 2012.
- 212 Heinz WJ, Grau A, Ulrich A, et al: Impact of benzodiazepines on posaconazole serum concentrations. A population-based pharmacokinetic study on drug interaction. *Curr Med Res Opin* 2012; 28(4):551-557. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 213 Product Information: NOXAFIL(R) oral suspension, posaconazole oral suspension. Schering Corporation (per FDA), Whitehouse Station, NJ, 2012.
- 214 Product Information: Zohydro(TM) ER oral extended-release capsules, hydrocodone bitartrate oral extended-release capsules. Zogenix, Inc. (per FDA), Emeryville, CA, 2013.
- 215 Product Information: AMBIEN(R) oral tablets, zolpidem tartrate oral tablets. Sanofi-Aventis US, LLC, Bridgewater, NJ, 2008.
- 216 Hoyumpa AM, Patwardhan R, Maples M, et al: Effect of short-term ethanol administration on lorazepam clearance. *Hepatology* 1981; 1:47-53.
- 217 Dorian P, Sellers EM, Kaplan HL, et al: Triazolam and ethanol interaction: kinetic and dynamic consequences. *Clin Pharmacol Ther* 1985; 37:558-562.
- 218 Guthrie SK & Lane EA: Reinterpretation of the pharmacokinetic mechanism of oral benzodiazepine ethanol interaction. *Alcoholism* 1986; 10:686-690.
- 219 Lister RG & File SE: Performance impairment and increased anxiety resulting from the combination of alcohol and lorazepam. *J Clin Psychopharmacol* 1983; 3:66-71.
- 220 File SE, Bond AJ, & Lister RG: Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* 1982; 2:102-106.
- 221 File SE, Bond AJ, & Lister RG: Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* 1982; 2:102-106.
- 222 Mattila MJ & Nuotto E: Caffeine and theophylline counteract diazepam effects in man. *Med Biol* 1983; 61:337-343.

- 223 Mattila MJ, Palva E, & Savolainen K: Caffeine antagonizes diazepam effects in man. *Med Biol* 1982; 60:121-123.
- 224 Product Information: Ativan(R) Injection, lorazepam. Wyeth, Philadelphia, PA, 2002.
- 225 Therapeutic Goods Administration: Prescribing medicines in pregnancy database. Therapeutic Goods Administration. Woden, Australian Capital Territory, Australia. 2011. Available from URL: <http://www.tga.gov.au/hp/medicines-pregnancy.htm>. As accessed 2011-06-20.
- 226 Martinez-Lage JF, Almagro MJ, & Hernandez FL: Aplasia cutis congenita of the scalp. *Childs Nerv Syst* 2002; 18:634-637.
- 227 McBride RJ & Dundee JW: A study of the plasma concentrations of lorazepam in mother and neonate. *Br J Anaesth* 1979; 51:971-978.
- 228 Whitelaw AGL & Cummings AJ: Effect of maternal lorazepam on the neonate. *Br Med J* 1981; 282:1106-1108.
- 229 McAuley DM & O'Neill MP: Lorazepam premedication for labour. *Br J Obstet Gynecol* 1982; 89:149-154.
- 230 Chesley S & Lumpkin M: Prenatal exposure to benzodiazepine--I. Prenatal exposure to lorazepam in mice alters open-field activity and GABAA receptor function. *Neuropharmacology* 1991; 30(1):53-58.
- 231 Autret E, Breteau M, Laugier J, et al: Pharmacocinetique et retentissement clinique chez le nouveau-ne des benzodiazepines consommees pendant la grossesse. *Journal de pharmacologie* 1985; 15:527.
- 232 Autret E, Rey E, Breteau M, et al: Retentissement neonatal de la consommation de benzodiazepines au cours de la grossesse. *Therapie* 1987; 42:305-310.
- 233 Gidai J, Acs N, Banhidy F, et al: Congenital abnormalities in children of 43 pregnant women who attempted suicide with large doses of nitrazepam. *Pharmacoepidemiol Drug Saf* 2010; 19(2):175-182. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 234 Weber LWD: Benzodiazepines in pregnancy-academical debate or teratogenic risk?. *Biological Res Pregn* 1985; 6:151-167.
- 235 Winter RM: In-utero exposure to benzodiazepines (letter). *Lancet* 1987; 1:627.
- 236 Czeizel A & Lendvay A: In-utero exposure to benzodiazepines. *Lancet* 1987; 1:628.
- 237 Gerhardsson M & Alfredsson L: In-utero exposure to benzodiazepines (letter). *Lancet* 1987; 1:628.
- 238 Laegreid L, Olegard R, Walstrom J, et al: Teratogenic effects of benzodiazepine use during pregnancy. *J Pediatr* 1989; 114:126-131.
- 239 Iqbal MM, Sobhan T, & Ryals T: Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatric Services* 2002; 53(1):39-49.
- 240 Product Information: Sonata(R), zaleplon capsules. Wyeth Laboratories, Philadelphia, PA, 2003.
- 241 Product Information: Ambien(R), zolpidem tartrate. Sanofi-Synthelabo Inc., New York, NY, 2002.
- 242 Anon: American academy of pediatrics committee on drugs: transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108(3):776-789.
- 243 Anon: Breastfeeding and Maternal Medication. World Health Organization, Geneva, Switzerland, 2002.
- 244 Whitelaw AGL, Cummings AJ, & McFadyen IR: Effect of maternal lorazepam on the neonate. *Br Med J Clin Res* 1981; 282:1106-1108.
- 245 Cummings AJ & Whitelaw AGL: A study of conjugation and drug elimination in the human neonate. *Br J Clin Pharmacol* 1981; 12:511-515.

- 246 Johnstone M: Effect of maternal lorazepam on the neonate. *Br Med J* 1981; 282:1973.
- 247 Johnstone MJ: The effect of lorazepam on neonatal feeding behaviour at term. *Pharmatherapeutica* 1982; 3:259-262.
- 248 Summerfield RJ & Nielsen MS: Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; 57:1042-1043.
- 249 Iqbal MM, Sobhan T, & Ryals T: Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatric Services* 2002; 53(1):39-49.
- 250 Leube H & Hoffkes H: Experience with the new tranquilizer Wy 4036 (lorazepam) in psychiatric-neurologic and internal medicine. *Arzneimittelforschung* 1971; 21:1098.
- 251 Anon: Sublingual use of benzodiazepines (letter). *Drug Intell Clin Pharm* 1985; 19:839-840.
- 252 Caille G, Spenard J, Lacasse Y, et al: Pharmacokinetics of two lorazepam formulations, oral and sublingual, after multiple doses.. *Biopharm Drug Dispos* 1983; 4(1):31-42.
- 253 Greenblatt DJ, Divoll M, Harmatz JS, et al: Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular and oral lorazepam. *J Pharm Sci* 1982; 71:248-252.
- 254 Kothary SP, Brown ACD, Pandit UA, et al: Time course of antirecall effect of diazepam and lorazepam following oral administration. *Anesthesiology* 1981; 55(6):641-644.
- 255 Banen DM & Resnick O: Lorazepam versus glutethimide as a sleep-inducing agent for the geriatric patient. *J Am Geriatr Soc* 1973; 21:507.
- 256 Goldbloom AL: The use of lorazepam in the management of seizures. *Pediatr Rev* 1990; 12:31.
- 257 Chamberlain JM, Capparelli EV, Brown KM, et al: Pharmacokinetics of intravenous lorazepam in pediatric patients with and without status epilepticus. *Journal of Pediatrics* 2012; 160(4):667-672. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 258 Kantarjian HM , Shah NP , Cortes JE , et al: Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood* 2012; 119(5):1123-1129. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 259 Product Information: Ativan(R), lorazepam. Wyeth, Philadelphia, PA, 2002.
- 260 Reynolds JEF (ed): Martindale: The Extra Pharmacopoeia (electronic version). Micromedex, Inc. Denver, CO. 1991.
- 261 Greenblatt DJ: Clinical pharmacokinetics of oxazepam and lorazepam. *Clin Pharmacokinet* 1981; 6:89-105.
- 262 Gram-Hansen P & Schultz A: Plasma concentrations following oral and sublingual administration of lorazepam. *Int J Clin Pharmacol Ther Toxicol* 1988; 26:323-324.
- 263 Hardman JG, Gilman AG, & Limbird LE Hardman JG, Gilman AG, & Limbird LE (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th. McGraw-Hill, New York, NY, 1996.
- 264 Product Information: ATIVAN intramuscular, intravenous powder for solution, lorazepam intramuscular, intravenous powder for solution. Baxter Healthcare Corporation, Deerfield, IL, nd.
- 265 Product Information: INTENSOL(TM) oral solution USP, lorazepam oral solution USP. Roxane Laboratories, Inc, Columbus, OH, 2003.
- 266 Product Information: ATIVAN(R) oral tablet, lorazepam oral tablet. Wyeth Laboratories, Philadelphia, PA, 2002.
- 267 Divoll M & Greenblatt DJ: Effect of age and sex on lorazepam protein binding. *J Pharm Pharmacol* 1982; 34:122-123.
- 268 Greenblatt DJ, Allen MD, Locniskar A, et al: Lorazepam kinetics in the elderly. *Clin Pharmacol Ther* 1979b; 26:103-113.



- 269 Greenblatt DJ, Allen MD, MacLaughlin DS, et al: Single and multiple dose kinetics of oral lorazepam in humans: the predictability of accumulation. *J Pharmacokinet Biopharm* 1979c; 7:159-179.
- 270 Ruelins HN: Comparative metabolism of lorazepam in man and four animal species. *J Clin Psychiatry* 1978; 39:11.
- 271 Kyriakoponlos AA, Greenblatt DJ, & Shader RI: Clinical pharmacokinetics of lorazepam: a review. *J Clin Psychiatry* 1978; 39:16-23.
- 272 Product Information: lorazepam oral tablet, USP, lorazepam oral tablet, USP. Watson Laboratories, Inc, Corona, CA, 2004.
- 273 Cummings AJ & Whitelaw AGL: A study of conjugation and drug elimination in the human neonate. *Br J Pharmacol* 1981; 12:511-515.
- 274 Greenblatt DJ, Shader RI, Franke K, et al: Pharmacokinetics and bioavailability of intravenous intramuscular and oral lorazepam in humans. *J Pharm Sci* 1979a; 68:57-63.
- 275 Greenblatt DJ & Miller LG: Mechanism of the anticonvulsant action of benzodiazepines. *Cleve Clin J Med* 1990; 57:S6-S8.
- 276 Crismon ML & Jann MW: Crismon ML & Jann MW: Anxiety and insomnia, in Young LY & Koda-Kimble MA (eds): *Applied Therapeutics The Clinical Use Of Drugs*, 4th. Applied Therapeutics, Vancouver, WA, 1988.
- 277 Haefely WE: Synaptic pharmacology of barbiturates and benzodiazepines. *Agents Actions* 1977; 7:353-359.
- 278 Soubrie P, Simon P, & Boissier JR: An amnesic effect of benzodiazepines in rats. *Experientia* 1976; 32:359.
- 279 Ameer B & Greenblatt DJ: Lorazepam: a review of its clinical pharmacological properties and therapeutic uses. *Drugs* 1981; 21:161-200.
- 280 Trissel LA, Xu QA, & Baker M: Drug compatibility with new polyolefin infusion solution containers. *Am J Health Syst Pharm* 2006; 63(23):2379-2382. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 281 Newton DW, Narducci WA, Leet WA, et al: Lorazepam solubility in and sorption from intravenous admixture solutions. *Am J Hosp Pharm* 1983; 40:424-427.
- 282 Stiles ML, Allen LV Jr, & Prince SJ: Stability of deferoxamine mesylate, floxuridine, fluorouracil, hydromorphone hydrochloride, lorazepam, and midazolam hydrochloride in polypropylene infusion-pump syringes. *Am J Health-Syst Pharm* 1996; 53:1583-1388.
- 283 Martens HJ, DeGoede PN, & Van Loenen AC: Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47:369-373.
- 284 Lowenstein DH & Alldredge BK: Status epilepticus. *N Engl J Med* 1998; 338(14):970-976.
- 285 Greenblatt DJ & Miller LG: Mechanism of the anticonvulsant action of benzodiazepines. *Cleve Clin J Med* 1990; 57:S6-S8.
- 286 Leppik IE: Status epilepticus (SE): the role of benzodiazepines. *Cleve Clin J Med* 1990; 57:S39-S44.
- 287 Tasker RC: Emergency treatment of acute seizures and status epilepticus. *Arch Dis Child* 1998; 79:78-83.
- 288 Carson SS, Kress JP, Rodgers JE, et al: A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; 34(5):1326-1332. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 289 McCollam JS, O'Neil MG, Norcross ED, et al: Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison. *Crit Care Med* 1999; 27(11):2454-2458.
- 290 Ihalaenen O, Viukari M, Jaaskelainen J, et al: Lorazepam, temazepam, placebo and assessment visits in psychiatric out-patients with anxiety. *Pharmatherapeutica* 1981; 2:628-636.

- 291 Linnoila M, Viukari M, Lamminsivu U, et al: Efficacy and side effects of lorazepam, oxazepam, and temazepam as sleeping aids in psychogeriatric inpatients. *Int Pharmacopsychiatr* 1980; 15:129-135.
- 292 Gringras M, Beaumont G, & Ankier SI: A comparison of the hypnotic activity of loprozalam, temazepam and placebo in general practice. *J Int Med Res* 1984; 12:10-16.
- 293 de Bruijn KM: Tropisetron: a review of the clinical experience. *Drugs* 1992; 43(Suppl 3):11-22.
- 294 Dogliotti L, Antonacci RA, Paze E, et al: Three years' experience with tropisetron in the control of nausea and vomiting in cisplatin-treated patients. *Drugs* 1992; 43(suppl 3):6-10.
- 295 Allen D, Curran HV, & Lader M: The effects of single doses of CL284,846, lorazepam, and placebo on psychomotor and memory function in normal male volunteers. *Eur J Clin Pharmacol* 1993; 45(4):313-320.
- 296 Schapira K, McClelland HA, & Newell DJ: A comparison of high- and low-dose lorazepam with amylobarbitone in patients with anxiety states. *Am J Psychiatry* 1977; 134:25-28.
- 297 Chierichetti SM, Moise G, Galeone M, et al: Beta-blockers and psychic stress: a double-blind, placebo-controlled study of bopindolol vs lorazepam and butalbital in surgical patients. *Int J Clin Pharmacol Ther Toxicol* 1985; 23:510-514.
- 298 Fontaine R, Chouinard G, & Annable L: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepine treatment. *Am J Psychiatry* 1984; 141:848-852.
- 299 Cordingley GJ, Dean BC, & Hallett C: A multi-centre, double-blind parallel trial of bromazepam ('Lexotan') and lorazepam to compare the acute benefit-risk ratio in the treatment of patients with anxiety. *Curr Med Res Opin* 1985; 9:505-510.
- 300 Ponnudurai R & Hurdley J: Bromazepam as oral premedication: a comparison with lorazepam. *Anesthesia* 1986; 41:541-543.
- 301 Murphy SM & Tyrer P: A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *Br J Psychiatry* 1991; 158:511-516.
- 302 Meehan K, Zhang F, David S, et al: A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* 2001; 21(4):389-397. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 303 Kearsley JH, Williams AM, & Fiumara AM: Antiemetic superiority of lorazepam over oxazepam and methylprednisolone as premedicants for patients receiving cisplatin-containing chemotherapy. *Cancer* 1989; 64:1595-1599.
- 304 Male CG & Johnson HD: Oral benzodiazepine premedication in minor gynaecological surgery. *Br J Anaesth* 1984; 56:499-507.
- 305 Myrick H, Malcolm R, Randall PK, et al: A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal. *Alcohol Clin Exp Res* 2009; Epub:-. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 306 Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; 298(22):2644-2653. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 307 Treiman DM, Meyers PD, Walton NY, et al: A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998; 339(12):792-798.
- 308 de Figueiredo R, Franchini A, Martinho A, et al: Differences in the effect of two benzodiazepines in the treatment of anxious outpatients. *Int Pharmacopsychiatr* 1981; 16:57-65.
- 309 Sacchetti E, Zerbini O, Banfi F, et al: Overlap of buspirone with lorazepam, diazepam and bromazepam in patients with generalized anxiety disorder: findings from a controlled, multicentre, double-blind study. *Hum Psychopharmacol* 1994; 9:409-422.

- 310 Pancheri P, Biondi M, Delle Chiaie R, et al: A study of the influence of chronic buspirone administration on the EEG spectral power of anxious patients. *New Trends Exp Clin Psych* 1990; VI(2):99-104.
- 311 Malcolm R, Myrick H, Roberts J, et al: The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. *J Gen Intern Med* 2002; 17(5):349-355.
- 312 Bertin I, Colombo G, Furlanut M, et al: Double-blind placebo cross-over study of long-acting (chlordesmethyldiazepam) versus short-acting (lorazepam) benzodiazepines in generalized anxiety disorders. *Int J Clin Pharm Res* 1989; 9:203-208.
- 313 Andreoli V, Maffei F, Montanaro N, et al: Double-blind cross-over clinical comparison of chlordesmethyldiazepam versus lorazepam in neurotic anxiety. *Arzneimittelforschung* 1977; 27:436-439.
- 314 Mansikka M, Kangas L, & Kanto J: A comparative study of the clinical effects of flunitrazepam and lorazepam. *Int J Clin Pharmacol Ther Toxicol* 1980; 18:320-321.
- 315 Scharf MB, Khosla N, Brocker N, et al: Differential amnestic properties of short- and long-acting benzodiazepines. *J Clin Psychiatry* 1984; 45:51-53.
- 316 Healey M, Pickens R, Meisch R, et al: Effects of clorazepate, diazepam, lorazepam, and placebo on human memory. *J Clin Psychiatry* 1983; 44:436-439.
- 317 Breitbart W, Marotta R, Platt MM, et al: A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996; 153:231-237.
- 318 Bieniek SA, Ownby RL, Penalver A, et al: A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy* 1998; 18:57-62.
- 319 Battaglia J, Moss S, Rush J, et al: Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; 15:335-340.
- 320 Kearsley JH, Williams AM, & Fiumara AM: Antiemetic superiority of lorazepam over oxazepam and methylprednisolone as premedicants for patients receiving cisplatin-containing chemotherapy. *Cancer* 1989; 64:1595-1599.
- 321 Haider I: A comparative trial of lorazepam and diazepam. *Br J Psychiatry* 1971; 119:599-600.
- 322 Singh AN & Saxena B: A comparison of lorazepam, diazepam and placebo in the treatment of anxiety states. *Curr Ther Res* 1974; 16:149-162.
- 323 Padron C: Comparative clinical evaluation of lorazepam and diazepam. *Praxis* 1974; 63:494.
- 324 Lawrence JM, Edwards JE, Briggs GS, et al: A controlled clinical trial of a new antianxiety agent lorazepam (Ativan(R)). *Med J Aust* 1974; 2:660-661.
- 325 Kasich AM: Lorazepam in the management of anxiety associated with chronic gastrointestinal disease: a double-blind study. *Curr Ther Res* 1976; 19:292-306.
- 326 Heisterkamp DV & Cohen PJ: The effect of intravenous premedication with lorazepam (Ativan(R)), pentobarbitone or diazepam on recall. *Br J Anaesth* 1975; 47:79-81.
- 327 Siassi I, Thomas M, & Vanov SK: Evaluation of the safety and therapeutic effects of lorazepam on long-term use. *Curr Ther Res* 1975; 18:163-171.
- 328 Eaves D, Kane K, & Swinson RP: A double-blind, controlled trial of lorazepam and diazepam in the treatment of anxiety. *Curr Med Res Opin* 1973; 1:265-268.
- 329 Scheliker J: A comparison of lorazepam and diazepam in general practice. *Curr Med Res Opin* 1973; 1:269-271.
- 330 Ananth J & Van den Steen N: Intramuscular lorazepam. *Neuropsychobiology* 1983; 9:139-141.

- 331 Conner JT, Katz RL, Bellville JW, et al: Diazepam and lorazepam for intravenous surgical premedication. *J Clin Pharmacol* 1978; 18:285-292.
- 332 Lowenstein DH & Alldredge BK: Status epilepticus. *N Engl J Med* 1998; 338(14):970-976.
- 333 Treiman DM, Meyers PD, Walton NY, et al: A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998; 339(12):792-798.
- 334 Leppik IE, Derivan AT, Homan RW, et al: Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983; 249:1452-1454.
- 335 Giang DW & McBride MC: Lorazepam versus diazepam for the treatment of status epilepticus. *Pediatr Neurol* 1988; 4:358-361.
- 336 Marill KA, Walsh MJ, & Nelson BK: Intravenous lorazepam versus dimenhydrinate for treatment of vertigo in the emergency department: a randomized clinical trial. *Ann Emerg Med* 2000; 36(4):310-319.
- 337 Wang RI, Stockdale SL, & Hieb E: Hypnotic efficacy of lorazepam and flurazepam. *Clin Pharmacol Ther* 1976; 19:191-195.
- 338 McClure DJ, Walsh J, Chang H, et al: Comparison of lorazepam and flurazepam as hypnotic agents in chronic insomniacs. *J Clin Pharmacol* 1988; 28:52-63.
- 339 Gordon CJ, Pazdur R, Ziccarelli A, et al: Metoclopramide versus metoclopramide and lorazepam: superiority of combined therapy in the control of cisplatin-induced emesis. *Cancer* 1989; 63:578-582.
- 340 Bishop JF, Wolf M, Matthews JP, et al: Randomized, double-blind, cross-over study comparing prochlorperazine and lorazepam with high-dose metoclopramide and lorazepam for the control of emesis in patients receiving cytotoxic chemotherapy. *Cancer Treat Rep* 1987; 71:1007-1011.
- 341 Pande A, Crockatt J, Feltner D, et al: Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *Am J Psychiatry* 2003; 160:533-540.
- 342 Anon: Pregabalin. *Drugs Fut* 2001; 26(8):817-820.
- 343 Pande AC, Crockatt JG, Janney DE, et al: Pregabalin treatment of generalised anxiety disorder (GAD): three randomised, placebo controlled trials. *Eur Psychiatry* 2000; 15:S244.
- 344 Perez-Rencon H, Alvarez-Rueda JM, & Trujillo A: A comparative double-blind study between ketazolam and lorazepam in the treatment of anxiety. *Can Ther Res* 1981; 29:936-942.
- 345 Musch B, Morselli PL, & Priore P: Clinical studies with the new anxiolytic alpidem in anxious patients: an overview of the European experiences. *Pharmacol Biochem Behav* 1988; 29:803-806.
- 346 Treiman DM, Meyers PD, Walton NY, et al: A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med* 1998; 339(12):792-798.
- 347 Kris MG, Gralla RJ, Clark RA, et al: Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: a double-blind, randomized trial. *Cancer* 1987; 60:2816-2822.
- 348 Kris MG, Gralla RJ, Clark RA, et al: Consecutive dose-finding trials adding lorazepam to the combination of metoclopramide plus dexamethasone: improved subjective effectiveness over the combination of diphenhydramine plus metoclopramide plus dexamethasone. *Cancer Treat Rep* 1985; 69:1262-1985.
- 349 Roila F, Basurto C, Bracarda S, et al: A pilot study of metoclopramide, dexamethasone, diphenhydramine, and lorazepam in prevention of nausea and vomiting in cisplatin-treated patients. *Oncology* 1990; 47:415-417.

- 350 Orzack MH, Friedman L, Dessain E, et al: Comparative study of the abuse liability of alprazolam, lorazepam, diazepam, methaqualone, and placebo. *Int J Addict* 1988; 23:449-467.
- 351 Rajmohan V, Sushil K, & Mohandas E: A double blind randomised comparison of chlordiazepoxide and lorazepam in alcohol withdrawal. *Asian J Psychiatr* 2013; 6(5):401-403. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 352 Gale G & Galloon S: Lorazepam as a premedication. *Can Anaesth Soc J* 1976; 23:22-29.
- 353 Peters CG & Brunton JT: Comparative study of lorazepam and trimeprazine for oral premedication in paediatric anaesthesia. *Br J Anaesth* 1982; 54:623-628.
- 354 Burtles R & Astley B: Lorazepam in children: a double-blind trial comparing lorazepam, diazepam, trimeprazine and placebo. *Br J Anaesth* 1983; 55:275-279.
- 355 Laws D, Ashford JJ, & Anstee JA: A multicentre double-blind comparative trial fluvoxamine versus lorazepam in mixed anxiety and depression treated in general practice. *Acta Psychiatr Scand* 1990; 81:185-189.
- 356 Rush CR, Higgins ST, Bickel WK, et al: Acute effects of triazolam and lorazepam on human learning, performance and subject ratings. *J Pharmacol Exp Ther* 1993; 264:1218-1226.
- 357 Simms SG, Rhodes VA, & Madsen RW: Comparison of prochlorperazine and lorazepam antiemetic regimens in the control of postchemotherapy symptoms. *Nursing Res* 1993; 42:234-239.
- 358 Lorizio A & Salsa F: The effectiveness of oral midazolam as a hypnotic compared with lorazepam. *Pharmacol Ther* 1986; 4:463-471.
- 359 McCollam JS, O'Neil MG, Norcross ED, et al: Continuous infusions of lorazepam, midazolam, and propofol for sedation of the critically ill surgery trauma patient: a prospective, randomized comparison. *Crit Care Med* 1999; 27(11):2454-2458.
- 360 Bradwejn J, Shriqui C, Koszycki D, et al: Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. *J Clin Psychopharmacol* 1990; 10:403-408.
- 361 Sorel L, Mechler L, & Harman TJ: Comparative trial of intravenous lorazepam and clonazepam in status epilepticus. *Clin Ther* 1981; 4:326-336.
- 362 Subramaney U, Brook S, & Berk M: A prospective randomised double-blind controlled study of the efficacy of lorazepam versus clothiapine in the control of acutely behaviourally disturbed patients. *S Afr Med J* 1998; 88:307-310.
- 363 Moreno I, Rosell R, Abad-Estevé A, et al: Randomized trial for the control of acute vomiting in cisplatin-treated patients: high-dose metoclopramide with dexamethasone and lorazepam as adjuncts versus high-dose alizapride plus dexamethasone and lorazepam. *Oncology* 1991; 48:397-402.
- 364 Moreno I, Rosell R, Abad A, et al: Comparison of three protracted antiemetic regimens for the control of delayed emesis in cisplatin-treated patients. *Eur J Cancer* 1992; 28A:1344-1347.
- 365 Molino A, Guglielmo L, Azzolini ME, et al: The antiemetic activity of high-dose metoclopramide and high-dose alizapride in combination with lorazepam in patients receiving cancer chemotherapy. A prospective, randomized, double-blind study. *Oncology* 1991; 48:111-115.
- 366 Shull HJ, Wilkinson GR, Johnson R, et al: Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; 84:420.
- 367 Greenblatt DJ: Pharmacokinetics in clinical medicine: oxazepam versus other benzodiazepines. *Dis Nerv Syst* 1975; 36:6.
- 368 Gilman AG, Goodman LS, Rall TW, et al (Eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th. Macmillan Publishing Co, New York, NY, 1985.

- 369 Greenblatt DJ & Shader RI: Drug therapy: benzodiazepines. *N Engl J Med* 1974; 291:1011.
- 370 Sonne J, Andreasen PB, Loft S, et al: Glucuronidation of oxazepam is not spared in patients with hepatic encephalopathy. *Hepatology* 1990; 11:951-956.
- 371 Anderson PO, Knoben JE, & Troutman WG: *Handbook of Clinical Drug Data*, 9th. Appleton & Lange, Stamford, CT, 1999.
- 372 Young LY & Koda-Kimble MA (Eds): *Applied Therapeutics: The Clinical Use of Drugs*, 6th. Applied Therapeutics, Inc, Vancouver, WA, 1995.
- 373 Verbeeck R: Biotransformation and excretion of lorazepam in patients with chronic renal failure. *Br J Clin Pharmacol* 1976; 3:1033.
- 374 Greenblatt DJ: Lorazepam kinetics in the elderly. *Clin Pharmacol Ther* 1979; 26:103.
- 375 Kraus JW: Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; 24:411.
- 376 Peppers MP: Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. *Pharmacotherapy* 1996; 16:49-58.
- 377 Bakti G, Fisch HU, Karlaganis G, et al: Mechanism of the excessive sedative response of cirrhotics to benzodiazepines: model experiments with triazolam. *Hepatology* 1987; 7:629-638.
- 378 Bass NM & Williams RL: Guide to drug dosage in hepatic disease. *Clin Pharmacokinet* 1988; 15:396-420.
- 379 Klotz U, Avant GR, Hoyumpa A, et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest* 1975; 55:347.
- 380 Andreasen PB, Hendel J, Greisen G, et al: Pharmacokinetics of diazepam in disordered liver function. *Eur J Clin Pharmacol* 1976; 10:115-120.
- 381 Rodighiero V: Effects of liver disease on pharmacokinetics (review). *Clin Pharmacokinet* 1999; 37:399-431.
- 382 Anon: Antihistamines and driving-related behavior: A review of the evidence for impairment. *Ann Emerg Med* 2000; 36(4):388-389.
- 383 Runge JW: NHTSA notes commentary: antihistamines and driving performance - an underrecognized issue in traffic safety. *Ann Emerg Med* 2000; 36:389-390.
- 384 Malone DC, Lawson KA, Smith DH, et al: A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99(1 Pt 1):22-27.
- 385 Skoner DP: Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001; 108(1 Suppl):S2- S8.
- 386 Simon PA: Acute and chronic rhinitis. In: Koda-Kimble MA, Young LY & Kradjan WA (eds). *Applied therapeutics: the clinical use of drugs*. Lippincott Williams & Wilkins, Philadelphia, PA::23-1 - 23-31, 2001.
- 387 Brown NJ & Roberts LJ: Histamine, bradykinin and their antagonists. In: Hardman JG, Limbird LE et al (eds). *The pharmacological basis of therapeutics*, 10th edition. McGraw-Hill Medical Publishing Division, New York, NY::645-668, 2001.
- 388 Meltzer EO: Performance effects of antihistamines.. *J Allergy Clin Immunol* 1990; 86(4 Pt 2):613-619.
- 389 Philpot EE: Safety of second generation antihistamines. *Allergy Asthma Proc* 2000; 21(1):15-20.
- 390 Biehl B: Effects of azatadine maleate on subjective appraisal and psychomotor functions relevant to driving performance. *Curr Med Res Opin* 1979; 6(1):62-69.



- 391 Betts T, Markman D, Debenham S, et al: Effects of two antihistamine drugs on actual driving performance. *Br Med J (Clin Res Ed)* 1984; 288(6413):281-282.
- 392 Irving A & Jones W: Methods for testing impairment of driving due to drugs. *Eur J Clin Pharmacol* 1992; 43:61-66.
- 393 Patat A, Stubbs D, Dunmore C, et al: Lack of interaction between two antihistamines, mizolastine and cetirizine, and ethanol in psychomotor and driving performance in healthy subjects. *Eur J Clin Pharmacol* 1995; 48(2):143-150.
- 394 Weiler JM, Bloomfield JR, Woodworth GG, et al: Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. *Ann Intern Med* 2000; 132(5):354-363.
- 395 Ray WA, Thapa PB, & Shorr RI: Medications and the older driver. *Clin Geriatr Med* 1993; 9(2):413-438.
- 396 Bhatt-Mehta V & Rosen DA: Sedation in children; current concepts. *Pharmacother* 1998; 18(4):790-807.
- 397 Goad RN & Webster D: Sedation, analgesia, and anesthesia issues in the pediatric patient. *Pediatr Podiat* 1997; 14(1):131-148.
- 398 Algren JT & Algren CL: Sedation and analgesia for minor pediatric procedures. *Pediatr Emerg Care* 1996; 12(6):435-441.
- 399 Sabatini ES: Pediatric cocktail (letter). *Hosp Pharm* 1985; 20:206.
- 400 American Pain Society: Principles of analgesic use in the treatment of acute pain and cancer pain. American Pain Society (fifth edition), 2003.
- 401 Rowe PC (Ed): *The Harriet Lane Handbook*, 11th. Year Book Medical Publishers, Chicago, IL, 1984.
- 402 Petrack E, Marx C, & Wright M: Intramuscular ketamine is superior to meperidine, promethazine, and chlorpromazine for pediatric emergency department sedation. *Arch Pediatr Adolesc Med* 1996; 150:676-681.
- 403 Basch E, Prestrud AA, Hesketh PJ, et al: Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2011; 29(31):4189-4198. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 404 Kris MG, Hesketh PJ, Somerfield MR, et al: American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. *J Clin Oncol* 2006; 24(18):2932-2947. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 405 Grunberg SM, Warr D, Gralla RJ, et al: Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. *Support Care Cancer* 2011; 19 Suppl 1:S43-S47. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 406 Grossman F: A review of anticonvulsants in treating agitated demented elderly patients. *Pharmacotherapy* 1998; 18(3):600-606.
- 407 Class CA, Schneider L, & Farlow MR: Optimal management of behavioural disorders associated with dementia. *Drugs Aging* 1997; 10(2):95-106.
- 408 Rabins PV, Blacker D, Rovner BW, et al: American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; 164(12 Suppl):5-56. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 409 U.S. Food and Drug Administration: Conventional Antipsychotics - Healthcare Professional Sheet text version. U.S. Food and Drug Administration. Rockville, MD. 2009. Available from URL: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm>. As accessed 2009-06-23.
- 410 Meeks TW & Jeste DV: Beyond the Black Box: What is The Role for Antipsychotics in Dementia?. *Curr Psychiatr* 2008; 7(6):50-65. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>



- 411 Lancot KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 1998; 59(10):550-561. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 412 Borson S & Raskind MA : Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer's disease. *Neurology* 1997; 48(5 Suppl 6):S17-S24. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 413 Mintzer JE, Hoernig KS, & Mirski DF: Treatment of agitation in patients with dementia. *Clin Geriatr Med* 1998; 14(1):147-175.
- 414 Verma SD, Davidoff DA, & Kambhampati KK: Management of the agitated elderly patient in the nursing home: the role of the atypical antipsychotics. *J Clin Psychiatry* 1998; 59(suppl 19):50-55.
- 415 Tariot PN: Treatment of agitation in dementia. *J Clin Psychiatry* 1999; 60(suppl):11-20.
- 416 Herrmann N: Valproic acid treatment of agitation in dementia. *Can J Psychiatry* 1998; 43:69-72.
- 417 Rita Moretti, MD, Universita degli Studi di Trieste
- 418 Pollock BG & Mulsant BH: Behavioral disturbances of dementia. *J Geriatr Psychiatry Neurol* 1998; 11:206-212.
- 419 Nyth AL, Gottfries CG, Lyby K, et al: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992; 86:138-145.
- 420 Nyth AL & Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. *Br J Psychiatry* 1990; 157:894-901.
- 421 Serra-Mestres J, Shapleske J, & Tym E: Treatment of palilalia with trazodone (letter). *Am J Psychiatry* 1996; 153:580-581.
- 422 Raskind MA, Cyrus PA, Ruzicka BB, et al: The effects of Metrifonate on the cognitive, behavioral, and functional performance of Alzheimer's Disease in patients. *J Clin Psychiatry* 1999; 60:318-325.
- 423 Shelton PS & Brooks VG: Estrogen for dementia-related aggression in elderly men. *Ann Pharmacother* 1999; 33:808-812.
- 424 Le A & Patel S: Extravasation of Noncytotoxic Drugs: A Review of the Literature. *Ann Pharmacother* 2014; Epub:Epub. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 425 Schummer W, Schummer C, Bayer O, et al: Extravasation injury in the perioperative setting. *Anesth Analg* 2005; 100(3):722-727. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 426 Cohan RH, Ellis JH, & Garner WL: Extravasation of radiographic contrast material: recognition, prevention, and treatment. *Radiology* 1996; 200(3):593-604. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 427 Upton J, Mulliken JB, & Murray JE: Major intravenous extravasation injuries. *Am J Surg* 1979; 137(4):497-506. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 428 Bellin MF, Jakobsen JA, Tomassin I, et al: Contrast medium extravasation injury: guidelines for prevention and management. *Eur Radiol* 2002; 12(11):2807-2812. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 429 Kumar RJ, Pegg SP, & Kimble RM: Management of extravasation injuries. *ANZ J Surg* 2001; 71(5):285-289. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 430 Brown AS, Hoelzer DJ, & Piercy SA: Skin necrosis from extravasation of intravenous fluids in children. *Plast Reconstr Surg* 1979; 64(2):145-150. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 431 Gaze NR: Tissue necrosis caused by commonly used intravenous infusions. *Lancet* 1978; 2(8086):417-419. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 432 Heckler FR: Current thoughts on extravasation injuries. *Clin Plast Surg* 1989; 16(3):557-563. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 433 Roberts JR: Cutaneous and subcutaneous complications of calcium infusions. *JACEP* 1977; 6(1):16-20. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 434 Heckler FR & McCraw JB: Calcium-related cutaneous necrosis. *Surg Forum* 1976; 27(62):553-555. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 435 Yosowitz P, Ekland DA, & Sharw RD: Peripheral intravenous infiltration necrosis. *Ann Surg* 1975; 182(5):553-556. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 436 Tjon JA & Ansani NT: Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; 34(10):1189-1192. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 437 Steinmann G, Charpentier C, O'Neill TM, et al: Liposuction and extravasation injuries in ICU. *Br J Anaesth* 2005; 95(3):355-357. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 438 MacCara ME: Extravasation: a hazard of intravenous therapy. *Drug Intell Clin Pharm* 1983; 17(10):713-717. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 439 Zenk KE: Management of intravenous extravasations. *Infusion* 1981; 5:77-79. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 440 Barry PJ, Gallagher P, Ryan C, et al: START (screening tool to alert doctors to the right treatment)--an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Ageing* 2007; 36(6):632-638. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 441 Gallagher P, Ryan C, Byrne S, et al: STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; 46(2):72-83. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 442 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria (Supplementary Data). *Age Ageing* 2008; 37(6):1.
- 443 American Geriatrics Society 2012 Beers Criteria Update Expert Panel: American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2012; 60(4):616-631. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 444 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008; 37(6):673-679. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 445 January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; Epub:Epub. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 446 Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128(16):e240-e327. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 447 Weber MA, Schiffrin EL, White WB, et al: Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J*

- Clin Hypertens (Greenwich) 2014; 16(1):14-26. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 448 Khanna D , Fitzgerald JD , Khanna PP , et al: 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012; 64(10):1431-1446. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 449 Hsieh C: Treatment of constipation in older adults. Am Fam Physician 2005; 72(11):2277-2284. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 450 Jneid H, Anderson JL, Wright RS, et al: 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2012; 126(7):875-910. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 451 Kearon C, Akl EA, Comerota AJ, et al: Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 suppl):e419S-e494S. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 452 Baldwin DS, Waldman S, & Allgulander C: Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol 2011; 14(5):697-710. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 453 Davidson JR: First-line pharmacotherapy approaches for generalized anxiety disorder. J Clin Psychiatry 2009; 70 Suppl 2:25-31. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 454 Schutte-Rodin S, Broch L, Buysse D, et al: Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; 4(5):487-504. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 455 Guerrant RL, Van Gilder T, Steiner TS, et al: Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001; 32(3):331-351. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 456 Talley NJ & Vakil N: Guidelines for the management of dyspepsia. Am J Gastroenterol 2005; 100(10):2324-2337. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 457 Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Bethesda, MD. 2013. Available from URL: [http://www.goldcopd.org/uploads/users/files/GOLD\\_Report\\_2013Feb13.pdf](http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013Feb13.pdf). As accessed 2014-08-12.
- 458 Bhatt DL, Scheiman J, Abraham NS, et al: ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2008; 118(18):1894-1909. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 459 Zhang W, Moskowitz RW, Nuki G, et al: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008; 16(2):137-162. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 460 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum 2002; 46(2):328-346. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 461 Lucas MG; Bedretdinova D; Bosch JLHR et al: Guidelines on urinary incontinence. European Association of Urology. Arnhem, Netherlands. 2014. Available from URL: [http://www.uroweb.org/gls/pdf/20%20Urinary%20Incontinence\\_LR.pdf](http://www.uroweb.org/gls/pdf/20%20Urinary%20Incontinence_LR.pdf). As accessed 2014-08-13.
- 462 World Health Organization (WHO): WHO's cancer pain ladder for adults. World Health Organization (WHO). Geneva, Switzerland. 2014. Available from URL: <http://www.who.int/cancer/palliative/painladder/en/>. As accessed 2014-08-12.
- 463 Schweizer E & Rickels K: Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. *Acta Psychiatr Scand* 1998; 98(suppl 393):95-101.
- 464 Lader M: Withdrawal reactions after stopping hypnotics in patients with insomnia. *CNS Drugs* 1998; 10(6):425-440.
- 465 Hardman JS, Rall TW, Nies AS, et al (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th. Pergamon Press, New York, NY, 1996.
- 466 Alexander B & Perry PJ: Detoxification from benzodiazepines: schedules and strategies *J sub Abuse Treat* 1991; 8:9-17. Detoxification from benzodiazepines: schedules and strategies *J sub Abuse Treat* 1991; 8:9-17.
- 467 Brenner PM, Wolf B, Rechlin Th, et al: Benzodiazepine dependence: detoxification under standardized conditions *Drug and Alcohol Dependence* 1991; 29:195-204. Benzodiazepine dependence: detoxification under standardized conditions *Drug and Alcohol Dependence* 1991; 29:195-204.
- 468 DuPont RL: A Physician's guide to discontinuing benzodiazepine therapy *West J Med* 1990; 152:600-603. A Physician's guide to discontinuing benzodiazepine therapy *West J Med* 1990; 152:600-603.
- 469 Rickels K, Case WG, Schweizer E, et al: Benzodiazepine dependence: management of discontinuation *Psychopharmacology Bulletin* 1990; 26:63-68. Benzodiazepine dependence: management of discontinuation *Psychopharmacology Bulletin* 1990; 26:63-68.
- 470 Morin CM, Bastien C, & Guay B: Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 2004; 161(2):332-342.
- 471 Voshaar RO, Gorgels W, Mol A, et al: Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry* 2003; 182:498-504.
- 472 Anon: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30(1):119-141.
- 473 Ballenger JC, Davidson JR, Lecrubier Y, et al: Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. *J Clin Psychiatry* 2004; 65:55-62.
- 474 McGregor C, Machin A, & White JM: In-patient benzodiazepine withdrawal: comparison of fixed and symptom-triggered taper methods. *Drug Alcohol Rev* 2003; 22(2):175-180.
- 475 Baillargeon L, Landreville P, Verreault R, et al: Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ* 2003; 169(10):1015-1020.
- 476 Rickels K, DeMartinins n, Rynn M, et al: Pharmacologic strategies for discontinuing benzodiazepine treatment. *J Clin Psychopharmacol* 1999; 19(6 suppl 2):12S- 16S.
- 477 Anderson KE, Bloomer JR, Bonkovsky HL, et al: Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; 142(6):439-450. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 478 European Porphyria Initiative: Recommendations for the use of drugs in the acute porphyrias (AIP, HCP, VP). European Porphyria Initiative. Available from URL: <http://www.porphyria-europe.org>. As accessed 2/13/06.

- 479 Moore MR & Hift RJ: Drugs in the acute porphyrias--toxicogenetic diseases. *Cell Mol Biol (Noisy-le-grand)* 1997; 43(1):89-94. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 480 Beers MH, Ouslander JG, Rollinger I, et al: Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991; 151(9):1825-1832. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 481 Beers MH: Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; 157(14):1531-1536. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 482 Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; 163(22):2716-2724. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 483 Chutka DS, Takahashi PY, & Hoel RW: Inappropriate medications for elderly patients. *Mayo Clin Proc* 2004; 79(1):122-139. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 484 Jano E & Aparasu RR: Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother* 2007; 41(3):438-447. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 485 Product Information: TRANXENE T-TAB(R) oral tablets, clorazepate dipotassium oral tablets. Lundbeck Inc, Deerfield, IL, 2010.
- 486 Product Information: LIBRIUM(R) oral capsules, chlordiazepoxide HCl oral capsules. Valeant Pharmaceuticals International, Costa Mesa, CA, 2005.
- 487 Product Information: XANAX(R) oral tablets, alprazolam oral tablets. Pharmacia & Upjohn Co (per FDA), New York, NY, 2011.
- 488 Product Information: XANAX(R) XR oral extended-release tablets, alprazolam oral extended-release tablets. Pharmacia & Upjohn Co (per FDA), New York, NY, 2011.
- 489 Product Information: KLONOPIN(R) TABLETS, KLONOPIN(R) WAFERS oral tablets, orally disintegrating tablets, clonazepam oral tablets, orally disintegrating tablets. Genentech USA, Inc, South San Francisco, CA, 2010.
- 490 Product Information: VALIUM(R) oral tablets, diazepam oral tablets. Roche Laboratories Inc, Nutley, NJ, 2008.
- 491 Product Information: estazolam oral tablets, estazolam oral tablets. Watson Laboratories, Inc., Corona, CA, 2008.
- 492 Product Information: DORAL(R) oral tablets, quazepam oral tablets. Questcor Pharmaceuticals, Inc., Union City, CA, 2007.
- 493 Product Information: DALMANE(R) oral capsules, flurazepam hydrochloride oral capsules. Valeant Pharmaceuticals North America, Aliso Viejo, CA, 2007.
- 494 Product Information: oxazepam oral capsule, oxazepam oral capsule. Actavis Elizabeth LLC, Elizabeth, NJ, 2007.
- 495 Product Information: Restoril(TM) oral capsules, temazepam oral capsules. Mallinckrodt Inc., Hazelwood, MO, 2010.
- 496 Product Information: HALCION(R) oral tablets, triazolam oral tablets. Pharmacia & Upjohn Company, New York, NY, 2008.
- 497 Trissel LA & Martinez JF: Compatibility of allopurinol sodium with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; 51:1792-1799.
- 498 Trissel LA, Williams KY, & Gilbert DL: Compatibility screening of linezolid injection during simulated Y-site administration with other drugs and infusion solutions. *J Am Pharm Assoc (Wash)* 2000; 40(4):515-519. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 499 Stiles ML, Allen LV Jr, Prince SJ, et al: Stability of dexamethasone sodium phosphate, diphenhydramine hydrochloride, lorazepam, and metoclopramide hydrochloride in portable infusion-pump reservoirs. *Am J Hosp Pharm* 1994; 51:514-517.
- 500 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, USA, 1988.
- 501 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, USA, 1988.
- 502 Chan P, Heatherly K, Kupiec TC, et al: Compatibility of caspofungin acetate injection with other drugs during simulated Y-site coadministration. *Int J Pharm Compd* 2008; 12(3):276-278.
- 503 Savitsky ME: Visual compatibility of neuromuscular blocking agents with various injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47:820-821.
- 504 Savitsky ME: Visual compatibility of neuromuscular blocking agents with various injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47:820-821.
- 505 Trissel LA & Bready BB: Turbidimetric assessment of the compatibility of taxol with selected other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49:1716-1719.
- 506 McGuire TR, Narducci WA, & Fox JL: Compatibility and stability of ondansetron hydrochloride, dexamethasone, and lorazepam in injectable solutions. *Am J Hosp Pharm* 1993; 50:1410-1414.
- 507 McGuire TR, Narducci WA, & Fox JL: Compatibility and stability of ondansetron hydrochloride, dexamethasone, and lorazepam in injectable solutions. *Am J Hosp Pharm* 1993; 50:1410-1414.
- 508 Product Information: Zofran(R), ondansetron. Glaxo Inc, Research Triangle Park, NC, 1999.
- 509 Trissel LA, Tramonte SM, & Grilley BJ: Visual compatibility of ondansetron hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991b; 48:988-992.
- 510 Product Information: Zofran(R), ondansetron. Glaxo Inc, Research Triangle Park, NC, 1999.
- 511 Trissel LA, Tramonte SM, & Grilley BJ: Visual compatibility of ondansetron hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991b; 48:988-992.
- 512 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 513 Min DI, Brown T, & Hwang GC: Visual compatibility of tacrolimus with commonly used drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49:2964-2966.
- 514 McGuire TR, Narducci WA, & Fox JL: Compatibility and stability of ondansetron hydrochloride, dexamethasone, and lorazepam in injectable solutions. *Am J Hosp Pharm* 1993; 50:1410-1414.
- 515 McGuire TR, Narducci WA, & Fox JL: Compatibility and stability of ondansetron hydrochloride, dexamethasone, and lorazepam in injectable solutions. *Am J Hosp Pharm* 1993; 50:1410-1414.
- 516 Savitsky ME: Visual compatibility of neuromuscular blocking agents with various injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47:820-821.
- 517 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 518 Personal Communication: Jose F Gonzalez, MD, Executive Director Medical Services. McNeil Pharmaceutical, Spring House, PA, November 6, 1990.
- 519 Parker WA: Physical compatibility of ranitidine HCl with preoperative injectable medications. *Can J Hosp Pharm* 1985; 38:160-161.
- 520 Parker WA: Physical compatibility of ranitidine HCl with preoperative injectable medications. *Can J Hosp Pharm* 1985; 38:160-161.



- 521 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 522 Singh BN , Dedhiya MG , Dinunzio J , et al: Compatibility of ceftaroline fosamil for injection with selected drugs during simulated Y-site administration. *Am J Health Syst Pharm* 2011; 68(22):2163-2169. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 523 Trusley C, Kupiec TC, & Trissel LA: Compatibility of micafungin injection with other drugs during simulated Y-site co-administration. *Int J Pharm Compound* 2006; 10(3):230-233.
- 524 Dear Healthcare Professional letter for OFIRMEV(TM) (acetaminophen). Cadence Pharmaceuticals, 04/27/2011.
- 525 Bashaw ED, Amantea MA, Minor JR, et al: Visual compatibility of zidovudine with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1988; 45:2532-2533.
- 526 Souney PF, Solomon MA, & Stancher D: Visual compatibility of cimetidine hydrochloride with common preoperative injectable medications. *Am J Hosp Pharm* 1984; 41:1840-1841.
- 527 Savitsky ME: Visual compatibility of neuromuscular blocking agents with various injectable drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47:820-821.
- 528 Trissel LA & Martinez JF: Visual, turbidimetric, and particle-content assessment of compatibility of vinorelbine tartrate with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1994; 51:495-499.
- 529 Trissel LA & Martinez JF: Compatibility of filgrastim with selected drugs during simulated Y-site administration. *Am J Hosp Pharm* 1994; 51:1907-1913.
- 530 Personal Communication: Denise A Farolino, PharmD, Medical Surveillance and Communications. Norwich Eaton Pharmaceuticals, Inc, September 11, 1990.
- 531 Brammer MK, Chan P, Heatherly K, et al: Compatibility of doripenem with other drugs during simulated Y-site administration. *Am J Health Syst Pharm* 2008; 65(13):1261-1265. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 532 Trissel LA & Martinez JF: Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52:2208-2212.
- 533 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 534 Trissel LA & Martinez JF: Compatibility of piperacillin sodium plus tazobactam with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1994; 51:672-678.
- 535 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 536 Turowski RC & Durthaler JM: Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991; 48:2181-2184.
- 537 Mayron D & Gennaro AR: Stability and compatibility of granisetron hydrochloride in IV solutions and oral liquids and during simulated Y-site injection with selected drugs. *Am J Health-Syst Pharm* 1996; 53:294-304.
- 538 Forman JK, Lachs JR, & Souney PF: Visual compatibility of acyclovir sodium with commonly used intravenous drugs during simulated Y-site injection. *Am J Hosp Pharm* 1987; 44:1408-1409.
- 539 Lober CA & Dollard PA: Visual compatibility of gallium nitrate with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1993; 50:1208-1210.
- 540 Lor E & Takagi J: Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; 47:157-159.



- 541 Trissel LA, Parks NPT, & Santiago NM: Visual compatibility of fludarabine phosphate with antineoplastic drugs, anti-infectives, and other selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991a; 48:2186-2189.
- 542 Baltz JK, Kennedy P, Minor JR, et al: Visual compatibility of foscarnet with other injectable drugs during simulated Y-site administration. *Am J Hosp Pharm* 1990; 47:2075-2077.
- 543 Lor E & Takagi J: Visual compatibility of foscarnet with other injectable drugs. *Am J Hosp Pharm* 1990; 47:157-159.
- 544 Trissel LA, Saenz CA, Ogundele OB, et al: Compatibility of fenoldopam mesylate with other drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 2003; 60:80-85.
- 545 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 546 Product Information: Ativan(R) injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 547 Trissel LA, Gilbert DL, & Martinez JF: Compatibility of propofol injectable emulsion with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54:1287-1292.
- 548 Trissel LA, Bready BB, Kwan JW, et al: Visual compatibility of sargramostim with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. *Am J Hosp Pharm* 1992; 49:402-406.
- 549 Akkerman SR, Zhang H, Mullins RE, et al: Stability of milrinone lactate in the presence of 29 critical care drugs and 4 i.v. solutions. *Am J Health-Syst Pharm* 1999; 56:63-68.
- 550 Veltri MA & Conner KG: Physical compatibility of milrinone lactate injection with intravenous drugs commonly used in the pediatric intensive care unit. *Am J Health-Syst Pharm* 2002; 59:452-454.
- 551 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 552 Product Information: Ativan(R) Injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 553 Trissel LA, Chandler SW, & Folstad JT: Visual compatibility of amsacrine with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1990; 47:2525-2528.
- 554 Trissel LA & Martinez JF: Compatibility of aztreonam with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52:1086-1090.
- 555 Riggs RM, English BA, Webster AA, et al: Fosphenytoin Y-site stability studies with lorazepam and midazolam hydrochloride. *International Journal of Pharmaceutical Compounding* 1999; 3(3):235-238.
- 556 Grillo JA & Barie PS: Precipitation of lorazepam during infusion of volumetric pump. *Am J Health-Syst Pharm* 1996; 53:1850.
- 557 Share MJ, Harrison RD, Folstad J, et al: Stability of lorazepam 1 and 2 mg/mL in glass bottles and polypropylene syringes. *Am J Health-System Pharm* 1998; 55:2013-2015.
- 558 Product Information: Ativan(R) injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 559 Personal Communication: Deborah EL Zuber, RPh, Parenteral Products Unit, Pharmacy Research & Development. Wyeth Laboratories, Philadelphia, PA, February 12, 1987.
- 560 Product Information: Ativan(R) injection compatibility charts. Wyeth-Ayerst Laboratories, Philadelphia, PA, 1988.
- 561 Personal Communication: Deborah EL Zuber, RPh, Parenteral Products Unit, Pharmacy Research & Development. Wyeth Laboratories, Philadelphia, PA, February 12, 1987.
- 562 Boullata JJ, Gelone SP, Mancano MA, et al: Precipitation of lorazepam infusion. *Ann Pharmacother* 1996; 30:1037-1038.
- 563 Share MJ, Harrison RD, Folstad J, et al: Share MJ, Harrison RD, Folstad J et al: Stability of lorazepam 1 and 2 mg/mL in glass bottles and polypropylene syringes. *Am J Health-System Pharm* 1998; 55:2013-2015.

- 564 Trissel LA, Gilbert DL, Martinez JF, et al: Compatibility of parenteral nutrition solutions with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54:1295-1300.
- 565 Institute for Safe Medication Practices: ISMP Medication safety alert. Use of tall man letters is gaining wide acceptance. Institute for Safe Medication Practices. Huntingdon Valley, PA. 2008. Available from URL: <http://www.ismp.org/>.
- 566 Institute for Safe Medication Practices: ISMP updates its list of drug name pairs with TALL man letters. Institute for Safe Medication Practices. Horsham, PA. 2010. Available from URL: <http://www.ismp.org/>. As accessed 2010-12-08.
- 567 Institute for Safe Medication Practices (ISMP): Safety Briefs: Drug names too close for comfort. *ISMP Medication Safety Alert!(R) Acute Care* 2012; 17(23):2-3.
- 568 Institute for Safe Medication Practices: ISMP's List of Confused Drug Names. Institute for Safe Medication Practices. Horsham, PA. 2009. Available from URL: <http://www.ismp.org/>. As accessed 2009-09-14.

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

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

---

End of Document

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