

DRUGDEX-EV 0229

MICROMEDEX

DRUGDEX® Evaluations
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DIAZEPAM

[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)** initial, 10 mg IM or IV; may give 5 to 10 mg in 3 to 4 hr if necessary [1]
b) initial, 10 mg ORALLY 3 to 4 times in first 24 hr, then 5 mg ORALLY 3 to 4 times daily as needed [2] [3]

2) Anxiety

- a)** 2 to 10 mg ORALLY 2 to 4 times a day depending on symptom severity [2] [3]
b) 2 to 10 mg IM or IV every 3 to 4 hr if needed depending on symptom severity [1]

3) Sedation, Premedication before surgery, [endoscopic procedures](#) and [cardioversion](#)

- a)** preoperative medication, 10 mg IM before surgery [1]
b) [endoscopic procedure](#), 10 mg or less IV immediately prior to procedure; MAX 20 mg OR 5 to 10 mg IM 30 min prior to procedure [1]

c) [cardioversion](#), 5 to 15 mg IV 5 to 10 min prior to procedure [1]

4) Seizure, Refractory, increased frequency

a) 0.2 mg/kg gel RECTALLY, may repeat in 4 to 12 hr if necessary; may use for up to 1 episode/5 days or 5 episodes/month [19]

5) Seizure; Adjunct

a) 2 to 10 mg ORALLY 2 to 4 times daily [2] [3]

b) severe, recurrent; initial, 5 to 10 mg IV every 10 to 15 min as necessary up to a MAX dose of 30 mg; may repeat in 2 to 4 hr if needed [1]

c) initial, 0.2 mg/kg RECTALLY (rounded up to available rectal dose available available), may repeat in 4 to 12 hours, no more than 1 episode every 5 days, and 5 episodes per month [19]

6) Skeletal muscle spasm; Adjunct

a) 2 to 10 mg ORALLY 3 to 4 times a day [2] [3]

b) initial, 5 to 10 mg IM or IV, then repeat in 3 to 4 hr if needed [1]

7) [Status epilepticus](#)

a) initial, 5 to 10 mg IV every 10 to 15 min up to a MAX dose of 30 mg; may repeat in 2 to 4 hr if needed [1]

b) Pediatric

1) Anxiety

a) initial, 1 to 2.5 mg ORALLY 3 to 4 times daily; increase gradually as needed [2] [3]

2) Seizure, Refractory, increased frequency

a) 2 to 5 years, 0.5 mg/kg gel RECTALLY, may repeat in 4 to 12 hr if necessary; may use for up to 1 episode/5 days or 5 episodes/month [19]

b) 6 to 11 years, 0.3 mg/kg gel RECTALLY, may repeat in 4 to 12 hr if necessary; may use for up to 1 episode/5 days or 5 episodes/month [19]

c) 12 years and older, 0.2 mg/kg gel RECTALLY, may repeat in 4 to 12 hr if necessary; may use for up to 1 episode/5 days or 5 episodes/month [19]

3) Seizure; Adjunct

a) 6 months or older, initial, 1 to 2.5 mg ORALLY 3 to 4 times daily, may increase gradually as needed [2] [3]

b) severe, recurrent; 30 days to 5 years of age, 0.2 to 0.5 mg IV slowly (preferred) OR IM every 2 to 5 min up to a MAX of 5 mg [1]

c) severe, recurrent; 5 years and older, 1 mg IV slowly (preferred) OR IM every 2 to 5 min up to MAX of 10 mg; repeat in 2 to 4 hr if necessary [1]

d) 2 to 5 years, initial, 0.5 mg/kg RECTALLY (rounded up to the manufactured unit dose available), may repeat in 4 to 12 hours, no more than 1 episode every 5 days, and 5 episodes per month [19]

e) 6 to 11 years, initial, 0.3 mg/kg RECTALLY (rounded up to the manufactured unit dose available), may repeat in 4 to 12 hours, no more than 1 episode every 5 days, and 5 episodes per month [19]

f) 12 years and older, initial, 0.2 mg/kg RECTALLY (rounded up to the manufactured unit dose available), may repeat in 4 to 12 hours, no more than 1 episode every 5 days, and 5 episodes per month [19]

4) Skeletal muscle spasm; Adjunct

a) 6 months or older, initial, 1 to 2.5 mg ORALLY 3 to 4 times daily, may increase gradually as needed [2] [3]

5) Status epilepticus

a) 30 days to 5 years of age, 0.2 to 0.5 mg IV slowly (preferred) OR IM every 2 to 5 min up to a MAX of 5 mg [1]

b) 5 years and older, 1 mg IV slowly (preferred) OR IM every 2 to 5 min up to MAX of 10 mg; repeat in 2 to 4 hr if necessary [1]

c) infants and children, 0.1 mg/kg up to a MAX of 0.3 mg/kg IV every 2 min; do not exceed a total dose of 5 mg in children aged 30 days to 5 years OR a total dose of 10 mg in children aged 5 years or older [53] [1]

3) Contraindications

a) acute narrow-angle glaucoma [84]

b) hypersensitivity to diazepam [84]

c) myasthenia gravis [84]

d) pediatric patients less than 6 months of age [84]

e) severe hepatic insufficiency [84]

f) severe respiratory insufficiency [84]

g) [sleep apnea syndrome](#) [84]

4) Serious Adverse Effects

a) [Neutropenia](#)

5) Clinical Applications

a) FDA Approved Indications

1) [Alcohol withdrawal syndrome](#)

2) Anxiety

3) Sedation, Premedication before surgery, [endoscopic procedures](#) and [cardioversion](#)

4) Seizure, Refractory, increased frequency

5) Seizure; Adjunct

6) Skeletal muscle spasm; Adjunct

7) [Status epilepticus](#)

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

[Diazepam](#)

C) Orphan Drug Status

1) [Diazepam](#) viscous rectal solution has been designated an orphan product for use in the intermittent control of acute seizure activity in selected, refractory patients.

D) Physicochemical Properties

1) Molecular Weight

a) 284.75 [416]

1.2] Storage and Stability

A) Preparation

1) Enteral route

a) **Diazepam** liquid is not recommended for enteral tube administration since it is absorbed into the plastic tubing [83].

2) Intramuscular route

a) Administration

1) Intramuscular injections must be administered deeply into muscle mass [1]

2) The intramuscular autoinjector is for IM use only; do not use intravenously [82]

3) To administer the intramuscular autoinjector, remove safety cap, place the black end on the mid outer thigh, push hard until injector functions, and withdraw after 10 seconds to deliver a fixed dose of 10 mg [82].

3) Intravenous route

a) Preparation

1) For IV preparation, do not mix or dilute with other solutions or drugs in the syringe or infusion flask [1].

b) Administration

1) Intravenous injection must be done slowly; do not administer faster than 5 mg/min [1]

2) Do not inject into small veins. If direct injection is not feasible, may inject through infusion tubing as close as possible to the vein insertion [1].

3) Avoid intra-arterial administration or extravasation [1].

4) Oral route

a) Administration

1) Only measure the oral concentrate using the calibrated dropper provided [81].

2) The oral concentrate may be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings and consume the entire mixture immediately [81].

5) Rectal route

a) Preparation

1) To prepare the rectal gel for dispensing, hold the barrel of the syringe, grasp the cap with other hand and set dose by turning until the dose can be viewed in the window. Push the

locking ring upward to lock-in the prescribed dose. Repeat the process with second syringe [19]

b) Administration

1) Remove the cap from the syringe and insure that the seal pin is removed with the cap. With the tip inserted into the rectum, push the plunger in over 3 seconds until it stops. Wait 3 seconds before removing the syringe from the rectum. Hold the buttocks together for 3 seconds, and keep the patient on their side to prevent leakage [19].

B) Intramuscular route

1) Solution

a) Store at controlled room temperature, 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees F (59 and 86 degrees F). Do not refrigerate [437].

b) Certain lots of the autoinjector, listed in the table below, may be used for up to 1 year beyond the manufacturer expiration date [438].

Lot Number	Manufacturer Original Expiration Date	New Use-by Date
9D1347	August 31, 2014	August 31, 2015
9D1666	July 31, 2014	July 31, 2015
9D1667	July 31, 2014	July 31, 2015
9DB731	August 31, 2014	August 31, 2015
9DY732	August 31, 2014	August 31, 2015
0D1093	December 31, 2014	December 31, 2015
0D1264	March 31, 2015	March 31, 2016
0D1460	April 30, 2015	April 30, 2016
0D1461	April 30, 2015	April 30, 2016
0D1462	April 30, 2015	April 30, 2016

C) Rectal route

1) Gel/Jelly

a) **Diastat(R)**, a gel formulation of **diazepam** in a plastic applicator for rectal administration, remained stable (retaining 95% or more of label strength) when tested at 24 months after storage temperatures above 30 degrees Celsius, at 8 months after storage at 40 degrees Celsius, at 1 month after storage at extreme light exposure, and after 3 freeze-thaw cycles. The restocking frequency of **Diastat(R)** in ambulances can be up to 48 months in nonfreezing environments, but the labeled expiration date should not be exceeded [439].

D) **Diazepam** stored in a clear glass syringe under ambient conditions in an ambulance in San Francisco retained 90% of its original concentration for up to 5 months [440]. For the first 4 months of the study, minimum temperature in the ambulances remained less than 20 degrees Celsius (C) and the maximum rarely exceeded 30 degrees C. During the summer months, however, the maximum temperatures frequently exceeded 30 degrees C.

E) **Diazepam** injectable emulsion should be stored at or below 25 degrees C; do not freeze. The **diazepam** emulsion can be exposed to temperature changes between 5 degrees C and 30 degrees C for a period of not more than 4 hours at least 20 times without deterioration [10].

- F) **Diazepam** injection repackaged as 5 milligrams doses in disposable glass syringes is chemically stable for 90 days when stored at 4 degrees Celsius or 30 degrees Celsius; however, refrigeration is suggested (Smith & Nuessel, 1982).
- G) When packaged in Tubex cartridges (5 milligrams per 1 to 2 milliliters) **diazepam** retained potency for 3 months at room temperature [441].

1) ADSORPTION

- a) When **diazepam** is administered by **continuous intravenous infusion**, variable drug delivery has been reported because of interaction with the infusion system [442] [443] [444] [445] [446]. It is not recommended that **diazepam** be admixed in solutions in plastic containers, stored in polyvinylchloride bags administered through plastic administration sets or mixed with drugs in a syringe as this may significantly reduce **diazepam** concentrations [90] [445] [447] [448]. If **diazepam** cannot be administered directly by an intravenous route then it may be injected slowly through the infusion tubing as close as possible to the vein insertion point [90]. **Diazepam** injectable emulsion should also not be added to infusion sets containing polyvinyl **chloride** [10]. Studies reveal that **diazepam** concentrations are reduced by 36% to 55% after infusion through administration sets stored for 2 hours in a PVC bag. The use of 0.45 micron inline filters did not cause a loss of potency [447]. Delivery of **diazepam** through a polyvinyl **chloride** (PVC) set was compared with delivery through a polyethylene-lined intravenous administration set. For infusion periods of up to 5 hours **diazepam** delivery through polyethylene-lined intravenous administration sets was superior to delivery through PVC sets (100.7% vs 65.4%) [449].
- b) **Diazepam** binds to PVC and, to a lesser degree, Stedim 6 bags [450]. The **adsorption** of **diazepam** 40 micrograms/milliliter in **Sodium chloride** 0.9% and 5% **dextrose** solutions was compared in PVC and Stedim 6 infusion bags and glass containers. The containers were stored at 20 degrees C for 24 hours in the daylight. No loss was measured in the glass containers. In the PVC bags, an 18% loss was seen in the 5% **dextrose** solution and a 25% loss was seen in the **Sodium chloride** 0.9% solution. In the Stedim 6 bags, a 6% loss was seen in both solutions. When the same solutions were stored for 72 hours, an 25% loss occurred in the 5% **dextrose** solution in PVC bags, and a 28% loss occurred in the **Sodium chloride** 0.9% solution [451]. A 10% loss occurred in both solutions in the Stedim 6 bags.
- c) The **adsorption** of **diazepam** 40 milligrams/liter 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 Celsius protected from light. In 24 hours less than 1% **diazepam** loss was detected in the glass container and less than 2% loss was detected in the laminate bag. However, greater than 54% **diazepam** loss was detected in the polyvinylchloride bag [452].
- d) The **adsorption** of **diazepam** was compared in glass containers, polyethylene containers, and PVC bags [453]. Over a 168-hour study period concentrations decreased 5% in polyethylene containers and up to 75% in PVC bags. Concentrations were virtually unchanged in glass. In a separate study, the authors determined that the percentage of **adsorption** was increased as the flow rate decreased.
- e) Equations and nomograms have been used to calculate the amount of **diazepam** adsorbed to different lengths of PVC tubing which can be used to calculate the dose of **diazepam** delivered to a patient during an intravenous infusion [453] [443].

f) No loss of potency was shown when **diazepam** was infused through a polybutadiene (PBD) administration set with a butadiene styrene (MBS) burette [454]. Losses in potency similar to other reports occurred with PVC infusion sets.

g) Loss of **diazepam** due to sorption is approximately 20% when plastic intravenous infusion sets are used. When a polyolefin-type tubing (Tridilset(R)) is used, drug loss is negligible [442].

h) **Diazepam** concentrations were almost unchanged after 24 hours when solutions (200 micrograms/milliliter) were made with **Dextrose** 5% in water or **Sodium chloride** 0.9% in glass or polyethylene bottles [455]. When the same solution was made in polyvinyl **chloride** bags, potency was reduced below 90% within 3.5 hours and 1 hour when mixed in **Dextrose** 5% in water or **Sodium chloride** 0.9% respectively. By the end of 24 hours, 37.4% and 42.8% of **diazepam** was lost from the **Dextrose** 5% in water or **Sodium chloride** 0.9% solutions, respectively.

i) If it is unavoidable, however, to store **diazepam** admixtures in PVC bags or administer through PVC tubing, measures should be taken to minimize the rate and extent of **diazepam** loss. This can be accomplished by decreasing the temperature and storage time and increasing the surface-area-to-volume ratio and the flow rate. The amount of **diazepam** actually delivered can be calculated with various equations [456].

2) Extemporaneous Formulation - Oral route

a) A **diazepam** 1 milligram/milliliter suspension, 80 milliliters, may be prepared using 8 **diazepam** 10 milligram tablets (**Valium**(R); Roche), absolute ethanol 4 milliliters, propylene glycol 24 milliliters, simple syrup 20 milliliters and chocolate syrup 32 milliliters. This mixture should be labeled "shake well" and "protect from light" and is stable for 14 days at room temperature [951].

b) A **diazepam** 1 milligram/milliliter suspension, 240 milliliters, may be prepared using 24 **diazepam** 10 mg tablets (**Valium**(R); Roche), distilled water to levigate, Cologel(R) (methylcellulose; Lilly) 80 milliliters and a sufficient quantity of a 2:1 simple syrup/cherry syrup mixture to bring the volume to 240 milliliters. This mixture should be labeled "shake well" and "refrigerate" and is stable for 60 days [952].

c) The following formula for preparing a **diazepam** suspension (1 milligram/milliliter) results in a suspension which is easily pourable and redispersible and is stable for at least 60 days at room or refrigerated temperature [953]:

INGREDIENT	QUANTITY
Diazepam 10 milligram tablets	10
Sucrose	55 grams
95% Ethanol	3.6 milliliters
Magnesium aluminum silicate	2 grams
Carboxymethylcellulose sodium medium viscosity	1 gram
Propylene glycol	5 milliliters
Raspberry flavor	
Red color	QS
Purified water	QS 100 milliliters

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Intramuscular route

1.3.1.A.1] Alcohol withdrawal syndrome

a) For acute alcohol withdrawal, the usual dose is 10 milligrams intramuscularly initially, then 5 to 10 milligrams in 3 to 4 hours if necessary [8].

1.3.1.A.2] Anxiety

a) For moderate anxiety: 2 to 5 milligrams intramuscularly, repeated in 3 to 4 hours if necessary [8]. For severe anxiety disorders, 5 to 10 milligrams intramuscularly; repeat every 3 to 4 hours as needed [8].

1.3.1.A.3] Sedation, Premedication before surgery, endoscopic procedures and cardioversion

a) Preoperative anxiety

1) As a preoperative medication to relieve anxiety and tension, the recommended dosage of diazepam is 10 milligrams intramuscularly before surgery [1].

1.3.1.A.4] Seizure; Adjunct

a) For severe recurrent convulsive seizures, 5 to 10 milligrams by intramuscular injection may be used; although, slow intravenous injection is the preferred route. The dose may be repeated every 10 to 15 minutes up to a maximum of 30 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

1.3.1.A.5] Skeletal muscle spasm; Adjunct

a) For muscle spasm associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus, the recommended dosage of diazepam is 5 to 10 milligrams (mg) intramuscularly, initially. If necessary, an additional 5 to 10 mg may be given after 3 to 4 hours. Larger doses may be needed for tetanus [8].

1.3.1.A.6] Skeletal muscle spasm - Tetanus

a) The recommended dose for the treatment of skeletal muscle spasms associated with tetanus is diazepam 5 to 10 milligrams intramuscularly. Repeat every 3 to 4 hours as necessary. Higher doses may be needed [1].

1.3.1.A.7) DOSE RANGE

a) Some data suggests bioavailability problems with the use of this route of administration (Hillestad et al, 1975a; Hillestad et al, 1975b) and the oral or intravenous route is preferred. Diazepam should be injected deeply into the muscle [8].

1.3.1.B] Intravenous route

1.3.1.B.1] Alcohol withdrawal syndrome

a) For acute alcohol withdrawal, the usual dose is 10 milligrams intravenously initially, then 5 to 10 milligrams in 3 to 4 hours if necessary [10] [8].

1.3.1.B.2] Anxiety

a) For moderate anxiety: 2 to 5 milligrams intravenously, repeated in 3 to 4 hours if necessary [8]. For severe anxiety disorders, 5 to 10 milligrams intravenously; repeat every 3 to 4 hours as needed [10] [8].

1.3.1.B.3] Sedation, Premedication before surgery, endoscopic procedures and cardioversion**a) Preoperative anxiety**

1) As a preoperative medication to relieve anxiety and tension, the recommended dose of diazepam emulsion is 10 milligrams intravenously before surgery [10].

2) For anesthesia, the usual dose is 2.5 to 20 milligrams intravenously slowly over 30 minutes; doses of 10 to 20 milligrams usually produces amnesia (Conner, 1977).

b) Endoscopic procedures

1) For endoscopic procedures, titrate intravenous dosage to desired sedative response prior to the procedure. Doses of 10 milligrams are usually adequate, but doses of 20 milligrams intravenous may be required in patients not receiving concurrent narcotic analgesics [1].

c) Cardioversion

1) For cardioversion, administer 5 to 15 milligrams by slow intravenous injection within 5 to 10 minutes prior to the procedure [1].

1.3.1.B.4] Seizure; Adjunct

a) For severe recurrent convulsive seizures, 5 to 10 milligrams by slow intravenous injection is recommended. The dose may be repeated every 10 to 15 minutes up to a maximum of 30 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

1.3.1.B.5] Skeletal muscle spasm; Adjunct

a) For muscle spasm associated with local pathology, cerebral palsy, athetosis, stiff-man syndrome or tetanus, the recommended dose of diazepam is 5 to 10 milligrams (mg) intravenously, initially. If necessary, an additional 5 to 10 mg may be given after 3 to 4 hours. Larger doses may be needed for tetanus [8] [10].

b) Diazepam was used as an infusion in the treatment of seizures associated with tetanus in a 31-year-old male [18]. Their results found that diazepam can be used successfully as an intravenous infusion (in lactated Ringers) in doses ranging from 5 milligrams/hour to 15 milligrams/hour, then gradually tapered and eventually replaced with oral diazepam.

1.3.1.B.6] Skeletal muscle spasm - Tetanus

a) The recommended dose for the treatment of skeletal muscle spasms associated with tetanus is diazepam 5 to 10 milligrams by slow intravenous injection. Repeat every 3 to 4 hours as necessary. Higher doses may be needed [1].

1.3.1.B.7] Status epilepticus

a) For the treatment of status epilepticus in adults, the initial dose is diazepam 5 to 10 milligrams (mg) intravenously. The dose may be repeated every 10 to 15 minutes up to a maximum total dose of 30 mg. Repeat in 2 to 4 hours if necessary [1].

- b) A dose of [diazepam](#) 0.15 milligram/kilogram (mg/kg) at a maximum infusion rate of 5 mg/minute followed by [phenytoin](#) 18 mg/kg has been utilized [60].

1.3.1.B.8) RATE OF ADMINISTRATION

a) IMPORTANT NOTE

1) DO NOT ADMINISTER AT RATES EXCEEDING 5 MILLIGRAMS/MINUTE TO AVOID [APNEA](#), VENOUS [THROMBOSIS](#), [PHLEBITIS](#) AND HYPOTENSION [8] [67]. Small veins such as those of the hand or wrist should not be used. Avoid intra-arterial administration or extravasation.

1.3.1.B.9) ADMIXTURES

- a) Addition of [diazepam](#) to intravenous solutions may result in precipitation of the drug, but may not be a problem depending upon solution and concentration (concentrations less than 10 mg/5 mL) [68].

1.3.1.C] Oral route

1.3.1.C.1] [Alcohol withdrawal syndrome](#)

- a) For acute alcohol withdrawal the usual oral dose is 10 milligrams 3 to 4 times during the first 24 hours, reducing to 5 milligrams three or four times a day as needed (Mayo-Smith et al, 1997) [8].
- b) [Diazepam](#) 10 to 20 milligrams orally was given every 1 to 2 hours (as a loading dose) until the withdrawal assessment scale (CIWA-A) was less than 10. The duration of [psychosis](#) secondary to ethanol was measured from the start of treatment until patients became asymptomatic. It was found that compared to the control group (standard [diazepam](#) dosing), the patients receiving [diazepam](#) loading dose had a substantial reduction in the duration of [delirium tremens](#) and [psychosis](#). The authors however, caution that individual assessment of patients before subsequent drug administration is required (Mayo-Smith et al, 1997) [9].

1.3.1.C.2] [Anxiety](#)

- a) The usual oral dose for treatment of anxiety is 2 to 10 milligrams two to four times a day [8].

1.3.1.C.3] [Seizure; Adjunct](#)

- a) As an adjunct in seizure disorders, 2 to 10 milligrams orally two to four times a day is recommended [2] [3].

1.3.1.C.4] [Skeletal muscle spasm; Adjunct](#)

- a) For skeletal muscle spasm the usual oral dose is 2 to 10 milligrams three to four times a day [8].

1.3.1.D] Rectal route

1.3.1.D.1] [Seizure, Refractory, increased frequency](#)

a) DOSE RANGE

1) A [diazepam](#) rectal gel formulation has been approved for the management of selected, refractory patients with [epilepsy](#), on stable regimens of anti-epilepsy drugs, who require intermittent use of [diazepam](#) to control bouts of increased seizure activity [36]. The recommended adult dose of [diazepam](#) rectal gel is 0.2 milligrams/kilogram. Since the drug is

provided in fixed, unit doses of 2.5, 5, 7.5, 10, 12.5, 15, 17.5 and 20 milligrams, the prescribed dose is obtained by rounding upward to the next available dose. The manufacturer provides the following recommended dose ranges:

Weight (kilograms)	Dose (milligrams)
14 to 25	5
26 to 37	7.5
38 to 50	10
51 to 62	12.5
63 to 75	15
76 to 87	17.5
88 to 111	20

2) It is recommended that the dosage be adjusted downward in elderly and debilitated patients to reduce the likelihood of ataxia or oversedation. The prescribed dose of [diazepam](#) rectal gel should be adjusted by the physician periodically to reflect changed in the patient's age or weight. The 2.5 mg dose may also be used as a partial replacement dose for patients who may expel a portion of the first dose [36].

3) A second dose of [diazepam](#) rectal gel, when needed, may be given 4 to 12 hours after the first dose. Recommended treatment frequency is no more than 5 episodes per month and no more than one episode every 5 days [36].

4) Rectal [diazepam](#) has been used to successfully control eclamptic convulsions when vein access is impossible and magnesium sulfate is not available [35]. An intravenous preparation of [diazepam](#) 20 milligrams (mg) in a 10-milliliter syringe is used. The needle is removed and the barrel is lubricated. Half of the syringe is inserted into the rectum and the contents discharged. With syringe left in place, the buttocks is held together for 10 minutes. An additional 10 mg is instilled if seizures are not controlled within 10 minutes. Depending on clinical response the 10 mg rectal dose is repeated every hour.

1.3.1.D.2] Seizure; Adjunct

a) As an adjunct in refractory cluster seizures, the recommended dose is initially 0.2 mg/kg rectally rounded up to 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, or 20 mg (the manufactured unit doses available). A second dose, may be administered in 4 to 12 hours. Do not treat more than 1 episode every 5 days, or 5 episodes per month [19].

1.3.1.E] Anesthesia management

1) A specific anesthetic regimen designed to reduce cardiovascular stimulation from [ketamine](#) is as follows: premedication with [diazepam](#) 10 milligrams orally, followed by [atropine](#) sulfate 0.4 milligram intravenously at induction; [anesthesia](#) is induced by [ketamine](#) 0.1% infusion (1.5 milligrams/kilogram in 3 minutes), with [diazepam](#) 5 milligrams being administered at the beginning of each minute (total, 15 milligrams); [atracurium](#) or tubocurarine 0.6 milligram/kilogram intravenously is given during the second minute; following intubation, ventilation is maintained with nitrous oxide/oxygen and a continuous maintenance infusion of [ketamine](#) 0.2 milligram/kilogram/hour is administered during the first hour with intermittent bolus doses of [diazepam](#) (5 milligrams every 30 minutes); during the second and subsequent hours, [ketamine](#) is reduced to 0.1 milligram/kilogram/hour with additional doses of [diazepam](#) 2.5 milligrams every 30 minutes [859].

1.3.1.F] Spasticity

See Drug Consult reference: SPASTICITY - DRUG THERAPY

1.3.2] Dosage in Renal Failure

A) No specific dosage adjustment is necessary in **RENAL INSUFFICIENCY** [69].

B) Patients receiving greater than 15 milligrams/day should be under observation, due to an accumulation of active metabolites which are excreted by the kidneys [70].

1.3.3] Dosage in Hepatic Insufficiency

A) Some evidence indicates that the metabolism of **diazepam** in patients with LIVER DISEASE is impaired and that the elimination half-life is prolonged [71] [72]. Because of reduced **diazepam** clearance in patients with **cirrhosis**, daily dosage should be reduced by about 50% [73].

B) Among the class as a whole, **LORAZEPAM**, **OXAZEPAM**, and **TEMAZEPAM** may be the benzodiazepines of choice for patients with liver disease. These 3 agents undergo glucuronide conjugation and their half-lives are only slightly altered in the presence of **hepatic dysfunction**. Other benzodiazepines may be used, but the dosage or dosing interval may need to be altered to compensate for impaired hepatic metabolism [74] [75] [76] [77] [78] [79].

1.3.4] Dosage in Geriatric Patients

A) Usual recommended initial oral dose is 2 to 2.5 milligrams once a day to twice a day initially; increase gradually as needed and tolerated [8].

1.3.5] Dosage Adjustment During Dialysis

A) No dosage adjustment appears to be necessary during **hemodialysis** [69] [70].

1.3.6] Dosage in Other Disease States**A) OBESITY**

1) In obese patients a delay in accumulation occurs during multiple dose administration (2 milligrams nightly for 30 days) [80]. The accumulation half-life of **diazepam** was significantly longer in obese subjects versus normal subjects (7.8 days vs 3.1 days); similarly, the accumulation half-life of desmethyldiazepam was prolonged significantly. The elimination half-life of **diazepam** was also prolonged in obese subjects (82 vs 32 hours), with no change in total metabolic clearance. The increased half-life is related to the large increase in volume distribution. These data indicate that obese subjects require a considerably longer time to achieve maximum or optimal drug effects as compared to normal weight individuals during multiple dose therapy. Similarly, therapeutic or adverse effects may persist for more prolonged periods in obese patients after discontinuing chronic therapy.

1.4] Pediatric Dosage**1.4.1] Normal Dosage****1.4.1.A] Intramuscular route****1.4.1.A.1] Seizure; Adjunct**

a) 30 DAYS TO 5 YEARS

1j) For severe recurrent convulsive seizures, 0.2 to 0.5 milligram by [intramuscular injection](#) may be used; although, slow intravenous administration is the preferred route. The dose may be repeated every 2 to 5 minutes up to a maximum of 5 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

b) 5 YEARS AND OLDER

1j) For severe recurrent convulsive seizures, 1 milligram by [intramuscular injection](#) may be used; although, slow intravenous administration is the preferred route. The dose may be repeated every 2 to 5 minutes up to a maximum of 10 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

1.4.1.A.2] Skeletal muscle spasm - [Tetanus](#)

a) INFANTS (over 30 days of age)

1j) The recommended dose for the treatment of skeletal muscle spasms associated with [tetanus](#) is [diazepam](#) 1 to 2 milligrams intramuscularly. Repeat every 3 to 4 hours as necessary [1].

b) CHILDREN (5 years or older)

1j) The recommended dose for the treatment of skeletal muscle spasms associated with [tetanus](#) is [diazepam](#) 5 to 10 milligrams intramuscularly. Repeat every 3 to 4 hours as necessary [1].

1.4.1.B] Intravenous route

1.4.1.B.1] Seizure; Adjunct

a) 30 DAYS TO 5 YEARS

1j) For severe recurrent convulsive seizures, 0.2 to 0.5 milligram by slow [intravenous injection](#) is recommended. The dose may be repeated every 2 to 5 minutes up to a maximum of 5 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

b) 5 YEARS AND OLDER

1j) For severe recurrent convulsive seizures, 1 milligram by slow [intravenous injection](#) is recommended. The dose may be repeated every 2 to 5 minutes up to a maximum of 10 milligrams. Treatment may be repeated in 2 to 4 hours if necessary [1].

1.4.1.B.2] Skeletal muscle spasm - [Tetanus](#)

a) INFANTS (over 30 days of age)

1j) The recommended dose for the treatment of skeletal muscle spasms associated with [tetanus](#) is [diazepam](#) 1 to 2 milligrams by slow [intravenous injection](#). Repeat every 3 to 4 hours as necessary [1].

b) CHILDREN (5 years or older)

1j) The recommended dose for the treatment of skeletal muscle spasms associated with [tetanus](#) is [diazepam](#) 5 to 10 milligrams by slow [intravenous injection](#). Repeat every 3 to 4 hours as necessary [1].

1.4.1.B.3] [Status epilepticus](#)

a) NEONATES

1j) A regimen for the treatment of **status epilepticus** in neonates of **diazepam** 0.15 to 0.5 milligram/kilogram by slow **intravenous injection** has been utilized [66].

b) INFANTS

1j) The dose for infants (30 days or older) is **diazepam** 0.2 to 0.5 milligram (mg) by slow **intravenous injection** every 2 to 5 minutes as needed up to 5 mg. Repeat in 2 to 4 hours if necessary [1].

2j) For infants, a dose of **diazepam** 0.1 milligrams/kilogram (mg/kg) up to a MAX of 0.3 mg/kg intravenously every 2 minutes is suggested. Do not exceed a total dose of 5 mg in infants and children aged 30 days to 5 years [53] [1].

c) CHILDREN

1j) For children older than 5 years, doses of **diazepam** 1 milligram (mg) every 2 to 5 minutes as needed up to 10 mg are recommended [1] [57] [59]. Repeat in 2 to 4 hours if necessary [1].

2j) A dose of **diazepam** 0.1 milligrams/kilogram (mg/kg) up to a MAX of 0.3 mg/kg intravenously every 2 minutes is suggested. Do not exceed a total dose of 5 mg in children up to 5 years OR 10 mg in children aged 5 years or older [53] [1].

1.4.1.B.4j) RATE OF ADMINISTRATION

a) **Diazepam** should be given slowly over a 3-minute period in a dosage not to exceed 0.25 milligram/kilogram. After an interval of 15 to 30 minutes the initial dosage may be repeated. If relief of symptoms is not obtained after a third dose, adjunctive therapy is recommended [8].

1.4.1.C] Oral route

1.4.1.C.1] Anxiety

a) The usual dose for treatment of anxiety is **diazepam** 1 to 2.5 milligrams three to four times a day. The dose may be increased gradually as needed [2] [3].

1.4.1.C.2] Seizure; Adjunct

a) As an adjunct in seizure disorders, 1 to 2.5 milligrams orally two to four times a day is recommended. Increase the dose gradually as needed [2] [3].

1.4.1.C.3] Skeletal muscle spasm; Adjunct

a) For skeletal muscle spasms in children over 6 months of age, the usual oral dose is 1 to 2.5 milligrams three to four times a day. Increase the dose gradually as needed [2] [3].

1.4.1.D] Rectal route

1.4.1.D.1] Seizure, Refractory, increased frequency

a) A **diazepam** rectal gel formulation has been approved for the management of selected, refractory patients with **epilepsy**, on stable regimens of anti-epilepsy drugs, who require intermittent use of **diazepam** to control bouts of increased seizure activity [36]. The recommended pediatric dose of **diazepam** rectal gel is 0.5 milligrams/kilogram (mg/kg) for children 2 through 5 years old, 0.3 mg/kg for children 6 through 11 years old, and 0.2 mg/kg for children 12 years and older. Since the drug is provided in fixed, unit doses of 5, 7.5, 10, 12.5, 15, 17.5 and 20 mg, the prescribed dose is obtained by

rounding upward to the next available dose. The manufacturer provided the following recommended dose ranges:

2 through 5 years old (0.5 milligrams/kilogram)	
Weight (kilograms)	Dose (milligrams)
6 to 10	5
11 to 15	7.5
16 to 20	10
21 to 25	12.5
26 to 30	15
31 to 35	17.5
36 to 44	20
6 through 11 years old (0.3 milligrams/kilogram)	
Weight (kilograms)	Dose (milligrams)
10 to 16	5
17 to 25	7.5
26 to 33	10
34 to 41	12.5
42 to 50	15
51 to 58	17.5
59 to 74	20
12 years and older (0.2 milligrams/kilogram)	
Weight (kilograms)	Dose (milligrams)
14 to 25	5
26 to 37	7.5
38 to 50	10
51 to 62	12.5
63 to 75	15
76 to 87	17.5
88 to 111	20

b) The prescribed dose of [diazepam](#) rectal gel should be adjusted by the physician periodically to reflect changed in the patient's age or weight. The 2.5 mg dose may also be used as a partial replacement dose for patients who may expel a portion of the first dose [36].

c) A second dose of [diazepam](#) rectal gel, when needed, may be given 4 to 12 hours after the first dose. Recommended treatment frequency is no more than 5 episodes per month and no more than one episode every 5 days [36].

d) Rectal administration of undiluted [diazepam](#) was simple, safe, and effective in the treatment of seizures when intravenous access could not be obtained [40]. A 1 cc disposable [insulin](#) syringe, inserted 4 to 5 cm into the rectum was recommended as the means to administer the 0.5 to 1 milligram/kilogram [diazepam](#) dose. Therapeutic levels were achieved in 5 to 10 minutes in most studies and continued from 15 minutes to 4 hours. Mild or no side effects were reported in the majority of studies.

e) Rectal [diazepam](#) (injected into the rectal lumen) was reported effective in the treatment of [status epilepticus](#) in 5 pediatric patients (11 months to 8 years of age) [41]. [Diazepam](#) was given either as a single dose or in 2 to 3 divided doses; [diazepam](#) injectable solution was administered into the rectal lumen through a soft plastic [intravenous catheter](#). In the 5 patients doses varied widely, from 0.16 milligram/kilogram (total dose) to 0.6 milligram/kilogram, because of physician reluctance to use the 0.5 milligram/kilogram dose for fear of inducing [respiratory depression](#) and because of unfamiliarity with proper rectal dosing of the drug. Seizure activity abated in all 5 patients within 1 to 35 minutes; however, in patients given 0.5 milligram/kilogram as a first dose, seizures ceased in 1 to 3 minutes and no [respiratory depression](#) was noted. In patients administered serial doses, seizure activity stopped as the total dose approached 0.5 milligram/kilogram. The rectal route of administration should be considered for [diazepam](#) when establishing an intravenous line is difficult or delayed. This method

also lends itself to pre-hospital management. The authors suggest initial doses of 0.5 milligram/kilogram.

1.4.1.D.2] Seizure; Adjunct

a) 2 TO 5 YEARS

1j) As an adjunct in refractory cluster seizures, the recommended dose for patients age 2 to 5 years, initially is 0.5 mg/kg rectally rounded up to 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, or 20 mg (the manufactured unit doses available). A second dose, may be administered in 4 to 12 hours. Do not treat more than 1 episode every 5 days, or 5 episodes per month [19].

b) 6 TO 11 YEARS

1j) As an adjunct in refractory cluster seizures, the recommended dose for patients age 6 to 11 years, initially is 0.3 mg/kg rectally rounded up to 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, or 20 mg (the manufactured unit doses available). A second dose, may be administered in 4 to 12 hours. Do not treat more than 1 episode every 5 days, or 5 episodes per month [19].

c) 12 YEARS AND OLDER

1j) As an adjunct in refractory cluster seizures, the recommended dose for patients 12 years and older, initially is 0.2 mg/kg rectally rounded up to 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, or 20 mg (the manufactured unit doses available). A second dose, may be administered in 4 to 12 hours. Do not treat more than 1 episode every 5 days, or 5 episodes per month [19].

1.4.1.E] Premedication for anesthetic procedure

See Drug Consult reference: PEDIATRIC SEDATION REGIMENS

1.4.2] Dosage in Renal Failure

Aj) No specific dosage adjustment is necessary in **RENAL INSUFFICIENCY** [69].

Bj) Patients receiving greater than 15 milligrams/day should be under observation, due to an accumulation of active metabolites which are excreted by the kidneys [70].

1.4.3] Dosage in Hepatic Insufficiency

Aj) Some evidence indicates that the metabolism of **diazepam** in patients with **LIVER DISEASE** is impaired and that the elimination half-life is prolonged [71] [72]. Because of reduced **diazepam** clearance in patients with **cirrhosis**, [73] recommend that daily dosage be reduced by about 50%.

1.4.4] Dosage Adjustment During Dialysis

Aj) No dosage adjustment appears to be necessary during **hemodialysis** [69] [70].

2.0] Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1] Onset and Duration

A) Onset

1) Initial Response

a) SEDATION, ORAL: 30 minutes (Hillestad et al, 1975b).

B) Duration

1) Single Dose

a) [Status epilepticus](#), intravenous: 15 to 30 minutes [391].

2.2] Drug Concentration Levels

A) Time to Peak Concentration

1) ORAL, IMMEDIATE RELEASE: 0.89 to 1.32 hours [392]; (Hillestad et al, 1975a).

2) ORAL, SLOW-RELEASE: 3.8 hours [395].

3) INTRAMUSCULAR: 1 hour (Hillestad et al, 1975a).

4) RECTAL, GEL: 1.5 hours [396].

5) INTRAVENOUS, INJECTABLE EMULSION: 8 minutes [394].

B) Area Under the Curve

1) 330 to 1530 ng/mL/h [392].

a) No significant differences were found in AUC's for [diazepam](#) following [Valium\(R\)](#) 5 mg three times a day and [Valrelease\(R\)](#) 15 mg every day [393].

b) Mean area under the curve was 4685 ng/mL/hr after [diazepam](#) injectable emulsion 10 mg intravenous [394].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) ORAL, SLOW-RELEASE: 98% [395].

a) The absolute bioavailability of [diazepam](#) rectal gel to [diazepam](#) injectable is 90% [396].

b) The absolute bioavailability of [diazepam](#) injectable emulsion as compared to an [intravenous injection](#) of [diazepam](#) was 93% [394].

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

a) 94% to 99% [397] [398].

1)) Protein binding is also significantly greater in males than in females [399] but is significantly less in patients with end-stage renal disease or nephrotic syndrome [400] [401].

2)) The unbound fraction of diazepam increase (1.6 to 3.2 fold) during labor or prior to caesarian section [402].

2) OTHER DISTRIBUTION SITES

a) TISSUES, rapidly and widely distributed (particularly brain and liver) [403].

b) PLACENTA, levels similar to maternal plasma [404].

1)) Diazepam can be detected in neonatal blood (arterial and venous) within 30 seconds of its IV administration to the mother [404]. Fetal concentrations may exceed maternal levels due to accumulation [405] [406]. Equilibration of maternal and fetal blood levels occurs within 10 minutes of drug administration [407]. It was estimated that 0.4 mg/kg fetal body weight is transferred to the fetus following diazepam administration [408].

c) CEREBROSPINAL FLUID, concentration is approximately 1.6% of the total plasma [diazepam](#) concentration ($r = 0.99$) [398].

d) SALIVA, concentrations are approximately 1.6% of plasma concentration (correlation not accurate enough to predict plasma concentrations from saliva concentrations) [398].

B) Distribution Kinetics**1) Distribution Half-Life**

a) 7 to 10 hours (Hillestad et al, 1975b) [403].

2) Volume of Distribution

a) 1.1 L/kg (0.7 L/kg to 3.4 L/kg) [397] [409].

1)) The following volume of distribution comparisons have been made: 1.65 L/kg for elderly male subjects vs 1.19 L/kg for young male subjects [410]; 2.81 L/kg for obese patients versus 1.53 L/kg for controls (Abernathy et al, 1981); 1.87 L/kg in young females versus 1.34 L/kg in young males [411] [410]; 2.46 L/kg in elderly females vs 1.38 L/kg in young females [410]; 81.8 L in Caucasians as compared to 53.9 L in Chinese volunteers [412].

2.3.3] Metabolism**A) Metabolism Sites and Kinetics**

1J) LIVER, extensive (Abernathy & Greenblatt, 1981).

BJ) Metabolites

1J) N-desmethyldiazepam, active [413].

2J) N-methyloxazepam ([temazepam](#)), active [413].

aJ) Both products are converted to [oxazepam](#) which is then conjugated with glucuronic acid before excretion [403].

2.3.4] Excretion

AJ) Kidney

1J) Renal Excretion (%)

aJ) 75% (Reynolds, 1996).

BJ) Other

1J) Plasma clearance rates are independent of age [417].

2.3.5] Elimination Half-life

AJ) Parent Compound

1J) ELIMINATION HALF-LIFE

aJ) 0.83 to 2.25 days [418] [419].

1J) Diazepam's half-life increases with age to 79 hours (range 37 to 169 hours) [420] [419].

2J) In newborn infants, diazepam is more slowly metabolized to desmethyldiazepam with a prolonged half-life of 22 to 54 hours and minimally if at all, hydroxylated to oxazepam. Active metabolites persist for at least 1 to 2 weeks. Hydroxylated metabolites are present in children and full-term infants over 2 weeks old [405] [421] [422].

3J) The elimination half-life of diazepam in obese patients was markedly delayed (95 hours as compared to 40 hours in the controls) [423].

4J) The half-life of diazepam in patients with end-stage renal disease is 37 hours versus 92 hours in controls [400].

BJ) Metabolites

1J) N-desmethyldiazepam, 40 to 100 hours [414]; (Hillestad et al, 1975b).

2J) Nordiazepam, 194 hours (range 67 to 533 hours) [420].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: No [414]

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.1] Contraindications

- A) acute [narrow-angle glaucoma](#) [84]
- B) hypersensitivity to [diazepam](#) [84]
- C) [myasthenia gravis](#) [84]
- D) pediatric patients less than 6 months of age [84]
- E) severe [hepatic insufficiency](#) [84]
- F) severe [respiratory insufficiency](#) [84]
- G) [sleep apnea syndrome](#) [84]

3.2] Precautions

- A) Neurologic:
- B) increased seizure frequency or severity may occur upon abrupt withdrawal when used as adjunct treatment of convulsive disorders [84]
- C) Psychiatric:
- D) -- psychotic patients; use not recommended [84]
- E) -- use caution in patients with severe, latent, or anxiety-associated depression as suicidal tendencies may be present [84]
- F) -- psychiatric and paradoxical reactions have been reported with benzodiazepine use, especially in children and elderly; discontinue if reactions occur [84]
- G) Reproductive:
- H) -- use with caution in pregnant patients during labor and delivery as fetal heart rate irregularities and adverse reactions may occur in neonate, such as hypotonia, poor sucking, [hypothermia](#), and [respiratory depression](#) [84]
- I) Respiratory:
- J) -- use caution in patients with [chronic respiratory insufficiency](#) due to risk of [respiratory depression](#); dose adjustment recommended [84]
- K) Other:
- L) -- use caution with history of alcohol or drug use [84]
- M) -- elderly or debilitated patients; dose adjustment recommended to prevent ataxia or oversedation [84]
- N) Concomitant use:
- O) -- alcohol or other CNS depressants not recommended [84]

3.3] Adverse Reactions**3.3.1] Cardiovascular Effects****3.3.1.A] Cardiac dysrhythmia**

1J) **Cardiac dysrhythmias** were seen in 7 (35%) diazepam-treated patients in a study of intravenous benzodiazepine use during oral surgery. Three groups of 20 patients were sedated with either intravenous diazepam 0.25 mg/kg (max 20 mg), lorazepam 0.05 mg/kg (max 3 mg), or midazolam 0.01 mg/kg (max 20 mg) preceding a local injection of 4% prilocaine without epinephrine. In the diazepam-treated patients, 7 incidences of **dysrhythmias** occurred; unifocal **ventricular premature beats** occurred 3 times, **nodal rhythm**, **atrial premature beats**, bradycardia, and **tachycardia** each occurred once. In the lorazepam group, there were 3 incidences of **tachycardia** and 1 of bradycardia. In the midazolam group, **tachycardia** occurred once and bradycardia occurred 3 times [86].

3.3.1.B] Compartment syndrome

1J) **Compartment syndrome** occurred in a patient who had received diazepam 10 mg by direct injection into the right antecubital fossa vein. Within 8 hours, the forearm was tense, tender, and swollen; ulnar, radial, and medial nerve dysfunction was noted; palmar skin was cyanotic; and sensation and grip strength had decreased. Wrist flexor and carpal ligaments were released by surgery and hand circulation and forearm skin color improved. Eventually, **dry gangrene** developed in all digits [87].

3.3.1.C] Hypotension

1J) Hypotension has been reported in patients using diazepam [84].

3.3.1.D] Thrombophlebitis

1J) **Thrombophlebitis** is associated with the use of intravenous diazepam [88]. It is suggested that **thrombophlebitis** may be minimized by the use of heparin or saline flushes, steroids, changing vein sites and diazepam dilutions. Venous **sequelae** were more likely to occur following IV administration into the dorsum of the hand than into the antecubital fossa [89]. Also, a longer duration of administration was associated with venous **sequelae**.

2J) **Diazepam** given intravenously has the potential of causing local irritation, **phlebitis**, or venous **thrombosis**. To prevent this, solutions should be given at a rate of no greater than 5 mg/min, small veins should not be used, and extravasation should be avoided [90]. Rapid administration of normal saline (1 mL/mg diazepam) following diazepam administration may reduce diazepam-induced **thrombophlebitis** [91].

3J) A 33-year old male received diazepam 5 mg IV as sedative for endoscopic retrograde cholepancreatography, and developed mild **phlebitis** 2 days later. Following local heat treatment, erythema, pain and warmth resolved after one week. **Penicillamine** 250 mg PO daily was initiated 2 weeks later, resulting in exacerbation of the **phlebitis**, which persisted for 2 weeks. **Phlebitis** recurred again upon repeated **penicillamine** administration. The authors speculate that **penicillamine** may have prevented subclinical healing of the **phlebitis** induced by diazepam [92].

3.3.1.E] Vasculitis

1J) A 50-year old woman developed bullous **vasculitis**, fever, and neutrophilia 2 days after beginning diazepam 40 milligrams (mg) daily and thioridazine. **Thioridazine** was discontinued and **methylprednisolone** was administered but the eruption progressed. **Diazepam** was then discontinued with resolution of fever and **vasculitis** improved over the next 2 months. Results of a **lymphocyte** blast transformation test were positive for diazepam [93].

3.3.1.F] Vasodilatation

1J) Incidence: 2%, rectal gel [19]

2)) Vasodilation has been reported in 2% of patients in the [diazepam](#) rectal gel group compared to 0% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.2] Dermatologic Effects

3.3.2.A] [Hyperpigmentation of skin](#)

1)) [Hyperpigmentation](#) has been reported in patients receiving [diazepam](#) following [dermabrasion](#) treatment. Darkening of the skin occurs only in the dermabraded area and resolves several weeks after drug discontinuation and application of [hydroquinone](#) ointment [121].

3.3.2.B] [Rash](#)

1)) Incidence: 3%, rectal gel [19]

2)) Rash has been reported in 3% of patients in the [diazepam](#) rectal gel group compared with 0% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.2.C] [Sweet's syndrome](#)

1)) [Acute febrile neutrophilic dermatosis \(Sweet's Syndrome\)](#) developed in a 70-year old man within 5 days of taking [diazepam](#) for a muscular lumbar contracture. Symmetric, bilateral, purple- red plaques with hemorrhagic blisters appeared on the outer aspects of his hands. He had high fever and severe arthralgias. Blood neutrophils were highly elevated. The symptoms could not be attributed to any underlying condition (such as infection, inflammatory or [immune disease](#), or neoplastic disorder). [Diazepam](#) was discontinued, [prednisone](#) was given for 2 weeks and then tapered. [Skin lesions](#) cleared within 10 days. At 10-month follow-up there was no cutaneous or hematologic recurrence [120].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] [Acidosis](#)

1)) A case of [lactic acidosis](#) was reported in a man receiving intravenous [diazepam](#) for alcohol withdrawal. The authors attributed the [acidosis](#) to propylene glycol toxicity. Propylene glycol is a common vehicle for [diazepam](#) [105].

2)) [Lactic acidosis](#) was reported in a patient receiving large intravenous doses of [diazepam](#) (up to 75 mg/ hour) for the treatment of [tetanus](#). Although the mechanism was unclear, the author suggested that the propylene glycol vehicle may have been responsible (Kapoor, 1981).

3.3.3.B] [Gynecomastia](#)

1)) [Gynecomastia](#) has been reported in men taking usual daily doses of [diazepam](#) [109]; (Bergman, 1981).

3.3.3.C] [Hypothermia](#)

1)) Animal studies have supported a dose dependent decrease in core body temperature associated with [diazepam](#); this effect appears to be mediated via [GABA \(gamma-aminobutyric acid\)](#) receptor sites [110]. [111] demonstrated enhanced [hypothermia](#) in diazepam-treated rats that were subsequently treated with [chlorpromazine](#).

2)) [Diazepam](#) has been reported to cause [hypothermia](#) in an elderly patient. However, this patient, who received a total dose of 86 milligrams over 1 week, was believed to be predisposed to the development of [hypothermia](#) by immobility and severe [cardiovascular disease](#) [112].

3.3.3.D] [Lipids abnormal](#)

1) Males taking benzodiazepines had an [HDL cholesterol](#) level 3.3 mg/dL lower than matched controls (p=0.038). Females had an [HDL cholesterol](#) level 2 mg/dL lower than controls, but the differences were not significant. Neither sex showed a significant difference in total cholesterol or [LDL cholesterol](#), but [triglyceride](#) levels were significantly higher. This study was conducted by the multicenter Lipid Research Clinic (LRC) and screened over 60,000 persons [113].

3.3.3.E] Somatrophic hormone adverse reaction

1) Both oral and IV [diazepam](#) are potent stimulators of the secretion of growth hormone (Syvalahti et al, 1975; Ajlauni & el Khateeb, 1980) [106]. However, tolerance to the growth hormone-releasing effect of [diazepam](#) occurs after administration of therapeutic doses for prolonged periods [107]. In contrast, [diazepam](#) administration in acromegalic patients resulted in no significant changes in growth hormone levels [108].

3.3.4] Gastrointestinal Effects

3.3.4.A] Constipation

1) Constipation has been reported in patients using [diazepam](#) [84].

3.3.4.B] Diarrhea

1) Incidence: 4%, rectal gel [19]

2) Diarrhea has been reported in 4% of patients in the [diazepam](#) rectal gel group compared with less than 1% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.4.C] Drug-induced gastrointestinal disturbance

1) Gastrointestinal disturbances have been reported in patients using [diazepam](#) [84].

3.3.4.D] Excessive salivation

1) [Excessive salivation](#) has been reported in patients using [diazepam](#) [84].

3.3.4.E] Xerostomia

1) Dry mouth has been reported in patients using [diazepam](#) [84].

3.3.5] Hematologic Effects

3.3.5.A] Neutropenia

1) There have been isolated reports of [neutropenia](#) [84].

3.3.5.B] Thrombocytopenia

1) Two cases of [diazepam](#)-induced [thrombocytopenia](#) were reported. In both cases, benzodiazepine-dependent antibodies with antiplatelet activity were identified using in vitro techniques. The diagnosis of [diazepam](#)-induced [thrombocytopenia](#) was confirmed by drug challenge in 1 patient who developed [purpura](#), gingival bleeding and hematuria within 6 hours of [diazepam](#) administration [85].

3.3.6] Hepatic Effects

3.3.6.A] Alkaline phosphatase raised

1J) Elevated [alkaline phosphatase](#) (ALP) levels have been reported in patients using [diazepam](#) [84].

3.3.6.BJ [ALT/SGPT level raised](#)

1J) Elevated alanine transaminase ([ALT](#)) levels have been reported in patients using [diazepam](#) [84].

3.3.6.CJ [AST/SGOT level raised](#)

1J) Elevated aspartate transaminase (AST) levels have been reported in patients using [diazepam](#) [84].

3.3.6.DJ [Hepatotoxicity](#)

1J) A case of [hepatic injury](#) after administration of [diazepam](#) was reported (Tedesco and Mills, 1982). A 45-year old male was hospitalized with a suspected [myocardial infarction](#) and administered [heparin](#) (6000 units every 4 hours) and [diazepam](#) (5 mg 3 times daily). On admission the physical examination and laboratory values were normal except for an elevated [aspartate aminotransferase](#) (AST) of 60 IU. There was no history of [jaundice](#) or exposure to hepatotoxins. Three days later, [heparin](#) was discontinued after the initial diagnosis of [myocardial infarction](#) was ruled out. AST was 110 IU at this time. The following day, the patient was started on [isoniazid](#) for [tuberculosis](#). One day later, both drugs were discontinued when the AST rose to 250 IU. AST, [alanine aminotransferase](#) (ALT) and [alkaline phosphatase](#) returned to normal within three days and remained stable. Ten days later, the patient was rechallenged with [diazepam](#) and within 48 hours, AST was 118 IU, [alkaline phosphatase](#) 105 IU, and [ALT](#) 95 Sigma Frankel units. [Diazepam](#) was discontinued. Liver biopsy revealed [focal necrosis](#) and intracellular [cholestasis](#). [Isoniazid](#) was restarted without an elevation in liver function tests when followed for 21 days after initiating therapy.

3.3.6.EJ [Jaundice](#)

1J) [Jaundice](#) has been reported with [diazepam](#) use [84].

3.3.7J [Immunologic Effects](#)

3.3.7.AJ [Anaphylaxis](#)

1J) A 60-year old female with [lymphadenopathy](#) and [non-Hodgkin's lymphoma](#) received an [IV injection](#) of [diazepam](#) in preparation for a [bone marrow aspiration](#) and immediately developed facial edema, stridor, and cyanosis. Establishment of an airway and treatment with [hydrocortisone](#) and antihistamines resulted in facial edema resolution within 36 hours. The author interpreted this reaction to be an [anaphylactic reaction](#) to [diazepam](#) [123].

2J) A possible [anaphylactic reaction](#) to [diazepam](#) occurred in a 28-year old female who was premedicated prior to a gynecological procedure with 10 mg of [diazepam](#) IM. Within 2 minutes the patient developed symptoms of tingling of the fingers and toes associated with macular [exanthema](#) of the gluteal region. This was followed by development of cramps in the patient's arms and legs followed by loss of consciousness. The patient's blood pressure reading was unobtainable and an EKG showed [sinus tachycardia](#). Following supportive care, the patient's condition was stabilized and erythema developed into urticarial wheals which gradually faded over several hours [124].

3.3.8J [Musculoskeletal Effects](#)

3.3.8.AJ [Hip fracture](#)

1J) An increased incidence of hip fracture was reported in elderly patients receiving psychotropic agents. The study was a case-control evaluation of 1021 patients with hip fracture compared to 5606 control patients. An increased risk of hip fracture was observed with the use of hypnotic/anxiolytic agents with

a long elimination half-life (greater than 24 hours), tricyclic antidepressants, and antipsychotic agents. Current users were defined as subjects who had received a prescription in the 30 day period prior to the admission date for the initial hospitalization. The long half-life hypnotic/anxiolytic agents studied were [lorazepam](#), [diazepam](#), [chlordiazepoxide](#) and barbiturates (excluding [phenobarbital](#)). The tricyclic antidepressants included [amitriptyline](#), [doxepin](#) and [imipramine](#); antipsychotic agents evaluated were [thioridazine](#), [haloperidol](#), [chlorpromazine](#) and [perphenazine/amitriptyline](#). In contrast, shorter-acting hypnotic-anxiolytic agents (half-life of 24 hours or less) were not associated with an increased risk of hip fracture in these patients. The most frequently used agents in this category were [diphenhydramine](#), [hydroxyzine](#) and [chloral](#) hydrate. The increased risk of hip fracture observed in this study was directly related to the doses of the drugs. Analysis for confounding by [dementia](#) did not alter the results. Additional studies are needed to confirm these results in this and other populations and to evaluate the effects of other psychotropic drugs that have less pronounced sedative effects [122].

3.3.8.B] Muscle weakness

1) Muscle weakness has been reported in patients using [diazepam](#) [84].

3.3.8.C] Spasticity

1) Increased muscle spasticity has been reported in patients using [diazepam](#) [84].

3.3.9] Neurologic Effects

3.3.9.A] Amnesia

1) A 23-year old male experienced [retrograde amnesia](#) after 3 days of [diazepam](#) 5 mg 3 times daily for back spasms. He was found sitting in a church believing that it was 14 months in the past. He was diagnosed as being in a fugue-like state with [retrograde amnesia](#). Within 24 hours, his symptoms resolved with amnesia of the event [94].

3.3.9.B] Ataxia

1) Ataxia has been reported in patients using [diazepam](#) tablets [84].

2) Ataxia was reported in 3% of patients in the [diazepam](#) rectal gel group compared to less than 1% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.9.C] Confusion

1) Confusion has been reported in patients using [diazepam](#) [84].

3.3.9.D] Dizziness

1) Dizziness has been reported in patients using [diazepam](#) [84].

2) Dizziness has been reported in 3% of patients in the [diazepam](#) rectal gel group compared to 2% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.9.E] Drug withdrawal seizure

1) Seizures appeared to be exacerbated in 6 children receiving frequent rectal bolus administration of [diazepam](#). Three patients exhibited cyclic recurrent seizures, usually with an interval of about 4 days while the other 3 patients had frequent seizures with a tendency to occur in cluster with a gap every few days. Fluctuating [diazepam](#) plasma levels may have contributed to the increase in cyclical seizures, causing

withdrawal seizures to occur. Symptoms improved when [diazepam](#) treatment was restricted and some cases a low dose benzodiazepine was continuously administered [104].

3.3.9.F] [Dysarthria](#)

1) [Dysarthria](#) has been reported in patients using [diazepam](#) [84].

3.3.9.G] [Dyssomnia](#)

1) Sleep disturbances have been reported in patients using [diazepam](#) [84].

3.3.9.H] [Headache](#)

1) Headache has been reported in patients using [diazepam](#) [84].

2) Headache has been reported in 5% of patients in the [diazepam](#) rectal gel group compared to 4% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.9.I] [Impaired cognition](#)

1) Administration of [diazepam](#) 5 mg orally 3 times daily produced no significant effect on short-term or long-term memory in a 2-week, double-blind, crossover study involving 16 patients (19 to 46 years of age) with [anxiety neurosis](#). In this study, the memory tests utilized were from the [Wechsler Memory Scale](#) and a smell matching test which is not a standard test of memory [95].

2) In a controlled study, [buspirone](#) in doses of 5 or 10 mg did not impair the immediate or delayed verbal free recall of word lists in anxious subjects. However, [diazepam](#) 5 mg did delay the free recall of word lists in these subjects without an effect on immediate recall. In this study, delayed recall was measured 20 minutes after reading a list of 16 non-categorized nouns at a rate of 1 word/2 seconds. Neither drug altered digit span performance, another test of immediate memory. These data suggest that [buspirone](#) may be less likely to alter memory function during daily activities than [diazepam](#) [96].

3) In a randomized, double-blind, parallel study, 40 patients undergoing oral surgery received either [midazolam](#) 15 mg PO followed 35 minutes later by IV saline placebo or placebo followed 35 minutes later by [diazepam](#) 10 mg IV. Both treatments induced significant amnesia for visual stimuli and for surgical events [97].

4) In a prospective controlled study 30 subjects were randomly assigned to one of 3 groups: chronic [diazepam](#) therapy (0.2 mg/kg/day) over 3 weeks, acute therapy consisting of placebo and a single dose of [diazepam](#) (0.2 mg/kg) and placebo alone given periodically. The memory and performance of the subjects were tested before treatment, throughout treatment, and 7 days post-treatment. This study confirms that [diazepam](#) interferes with the acquisition of new information, thus impairing memory function. Acute use of the drug has the most effect on memory; however, a partial tolerance to [memory impairment](#) does develop after chronic use. After discontinuing [diazepam](#), memory function is restored. [Diazepam](#) does not appear to affect other performance or psychomotor tasks [98].

5) The effects of [diazepam](#) on spatial visualization were studied. In a double-blind crossover study, 12 healthy adult men were given [diazepam](#) 10 mg or placebo the evening before experimental testing, followed by 10 mg of [diazepam](#) or placebo at breakfast on the day of testing. All subjects had multiple practice sessions with the mental rotation task. Testing consisted of determining if a pair of two-dimensional geometric figures were identical or mirror images. Results showed the [diazepam](#) group to have a slowed reaction time in the task. The conclusion of the authors was that [diazepam](#) impairs the speed of spatial visualization [99].

3.3.9.J] [Impaired psychomotor performance](#)

1J) [Diazepam](#) affected neuromuscular processing related to balance control in 12 elderly, healthy volunteers. One hour after ingesting [diazepam](#) 0.14 mg/kg, anterior tibialis muscle latency was tested. Electrodes were applied to the right anterior tibialis muscle, and subjects stood on a horizontally perturbable platform. Latency was defined as the time from the onset of platform motion to the first burst of muscle activity. The anterior tibialis muscle activation latency was longer with [diazepam](#) as compared with placebo at 1 hour after administration by an average of 7.4 milliseconds (p less than 0.01). This suggests that [diazepam](#) slows the neural transmission of the response signal directly, which lengthens the automatic motor response at the spinal level. Since this response is via spinal reflex and not with conscious control, this represents another effect of [diazepam](#) in addition to cognitive slowing or sedation [101].

2J) [Diazepam](#) has been shown to impair driving performance under controlled laboratory tests [102]. In a sophisticated study of actual long distance night-time driving, either 10 mg [diazepam](#), 5 mg [diazepam](#), placebo, or no drug was given 1 hour before driving twice around a 50 km highway course [103]. Treatment regimens were randomized and administered under double-blind condition; all subjects drove under all treatment regimens on consecutive weeknights, when possible. The results showed that [diazepam](#) 10 mg significantly impaired the ability of the drivers to maintain the car in a straight line along the highway when compared to placebo or no drug, although [diazepam](#) 5 mg did not effect lateral position control of the automobile.

3.3.9.K] Incoordination

1J) Incidence: 3%, rectal gel [19]

2J) Incoordination has been reported in 3% of patients in the [diazepam](#) rectal gel group compared to 0% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.9.L] Insomnia

1J) Insomnia has been reported in patients using [diazepam](#) [84].

3.3.9.M] Normal auditory evoked potential, Mid-latency

1J) Intravenous induction of general [anesthesia](#) with [diazepam](#) 0.3 to 0.4 mg/kg in 10 subjects did not affect mid-latency auditory evoked potentials. This finding indicates that primary cortical processing of auditory stimuli is preserved when [diazepam](#) is used for [anesthesia induction](#) [100].

3.3.9.N] Slurred speech

1J) Slurred speech has been reported in patients using [diazepam](#) [84].

3.3.9.O] Somnolence

1J) Somnolence was reported in 23% of patients in the [diazepam](#) rectal gel group compared to 8% in the placebo group in two double-blind, placebo controlled studies [19].

2J) Drowsiness has been reported in patients using [diazepam](#) tablets [84].

3.3.9.P] Tremor

1J) Tremor has been reported in patients using [diazepam](#) [84].

3.3.9.Q] Vertigo

1J) Vertigo has been reported in patients using [diazepam](#) [84].

3.3.10] Ophthalmic Effects

3.3.10.A] Blurred vision

1) Blurred vision has been reported in patients using [diazepam](#) [84].

3.3.10.B] Diplopia

1) [Diplopia](#) has been reported in patients using [diazepam](#) [84].

2) Horizontal [diplopia](#) at a distance was reported by a 77-year old male patient within a few days of starting [diazepam](#) 2 mg 3 times daily and [prazosin](#) 0.5 mg 2 times daily. The [diplopia](#) developed each day 30 to 40 minutes after taking the morning dose of both drugs and continued all day. Divergence paralysis was diagnosed. The [diplopia](#) resolved the day after [diazepam](#) was withdrawn. There was no rechallenge [114].

3.3.11] Otic Effects**3.3.11.A] Ototoxicity**

1) Protracted tinnitus was described in 3 patients after discontinuation of chronic [diazepam](#) therapy (up to 30 mg daily for several years). In one patient, one year follow-up demonstrated persistent mild tinnitus despite [diazepam](#) abstinence. The use of very low-dose benzodiazepines may be useful for long-term management of these patients, especially if tinnitus is impairing the quality of life. Gradual tapering of the dose may also be helpful in chronic users to help minimize these symptoms [127].

3.3.12] Psychiatric Effects**3.3.12.A] Abnormal behavior**

1) An [obsessive-compulsive disorder](#) has been described following [diazepam](#) withdrawal. A 32-year old female was taking oral [diazepam](#) 6 mg/day for 7 years and discontinued therapy without tapering the dose. Within 2 weeks, the patient developed anxiety, hyperacusis, insomnia, and nightmares; the symptoms persisted and [obsessive-compulsive behavior](#) developed 4 weeks after [diazepam](#) was discontinued. The patient had no previous medical history of such behavior nor a family history of psychiatric disorders. The condition persisted for 10 months with the exception of a 2-week period when the [diazepam](#) was resumed, and discontinuation of the drug a second time prompted the return of the symptoms with increased severity. [Behavioral modification](#) caused significant improvement for the patient [125].

3.3.12.B] Aggressive behavior

1) Aggression has been reported in patients using [diazepam](#) [84].

3.3.12.C] Agitation

1) Agitation has been reported in patients using [diazepam](#) [84].

3.3.12.D] Anxiety

1) Anxiety has been reported in patients using [diazepam](#) [84].

3.3.12.E] Capgras' syndrome

1) [Diazepam](#) has been linked to [Capgras Syndrome](#) (a delusion that identical- appearing impostors have replaced familiar people) in a 78-year old man treated for the past 30 years with [diazepam](#) (5 mg twice daily) for general anxiety disorder. He was also receiving [paroxetine](#) 40 mg daily, [levothyroxine](#), [rabeprazole](#), [ranitidine](#), and [finasteride](#). He thought his sister-in-law had disguised herself as his wife and was now living

at his home; he even tried to remove his wife from the home. Upon hospitalized, [diazepam](#) was stopped and [risperidone](#) 0.5 mg four times daily started. Within 10 days, the delusion resolved [126].

3.3.12.F] Delusions

1) Delusions have been reported in patients using [diazepam](#) [84].

3.3.12.G] Depression

1) Depression has been reported in patients using [diazepam](#) [84].

3.3.12.H] Euphoria

1) Incidence: 3%, rectal gel [19]

2) Euphoria has been reported in 3% of patients in the [diazepam](#) rectal gel group compared with 0% of patients in the placebo group in parallel-group, placebo-controlled trials [19].

3.3.12.I] Hallucinations

1) Hallucinations have been reported in patients using [diazepam](#) [84].

3.3.12.J] Irritability

1) Irritability has been reported in patients using [diazepam](#) [84].

3.3.12.K] Nightmares

1) Nightmares have been reported in patients using [diazepam](#) [84].

3.3.12.L] Psychotic disorder

1) [Psychoses](#) have been reported in patients using [diazepam](#) [84].

3.3.12.M] Restlessness

1) Restlessness has been reported in patients using [diazepam](#) [84].

3.3.13] Renal Effects

3.3.13.A] Incontinence

1) Incontinence has been reported in patients using [diazepam](#) [84].

3.3.13.B] Urinary retention

1) Urine retention has been reported in patients using [diazepam](#) [84].

3.3.14] Reproductive Effects

3.3.14.A] [Breast cancer](#)

1) The use of [diazepam](#) has not been associated with an increased risk of [breast cancer](#) relative to other [cancers](#). The incidence was evaluated in a study which involved 1236 women with [breast cancer](#) and 728 control subjects with other malignancies. The relative risk for [breast cancer](#) in women who used the drug at least four days per week for at least six months was estimated to be 0.9, with a 95% confidence limit of 0.5 to 1.6 when compared to women who never used [diazepam](#). There was no obvious association between

recent use or use in the distant past and the incidence of [breast cancer](#). This would suggest that [diazepam](#) was not responsible for an increased incidence of [breast cancer](#), since the risk should be higher in recent users [128].

3.3.14.B] Sexual dysfunction

1) Libido changes have been reported with [diazepam](#) [84].

3.3.15] Respiratory Effects

3.3.15.A] Respiratory depression

1) In children presenting to a hospital with seizures, 9% were found to have [respiratory depression](#) following the use of [diazepam](#). There were 122 patient episodes with 94 children receiving [diazepam](#). [Respiratory depression](#) was seen in 11 patients with 8 requiring ventilation [115].

2) During peroral [endoscopic procedures](#), coughing, depressed respiration, dyspnea, and hyperventilation have been reported [90].

3) Patients at high-risk for developing [respiratory depression](#) include the following: 1) patients with [hepatic failure](#) who are receiving drugs which are primarily metabolized in the liver (eg, [diazepam](#)); 2) patients with underlying [pulmonary disease](#), including chronic [bronchitis](#), long-standing [airway obstruction](#), and chronic compensated respiratory failure; 3) and those concurrently receiving other drugs which depress ventilatory function (eg, narcotics). In addition, patients receiving intravenous [diazepam](#) prior to minor surgical and/or exploratory procedures such as [endoscopy](#), [needle biopsy](#), or dental procedures appear to be at high risk [116].

4) Oral [diazepam](#) 20 mg resulted in significant depression of upper airway reflexes in 10 healthy male subjects in a single-dose, placebo-controlled, double-blind, crossover study [117]. Upper airway reflex sensitivity (UARS) was measured using ammonia vapor as a chemical stimulus, and reaction time to an auditory stimulus (ART) was measured. There was significant depression of UARS between 30 and 150 minutes after [diazepam](#) administration; UARS returned to baseline levels within 210 minutes. As measured by ART, the major sedative effect of oral [diazepam](#) also occurred between 30 and 150 minutes. Murphy et al conclude that oral [diazepam](#) should be given 30 to 160 minutes before [anesthesia induction](#) in order to most effectively depress upper airway reflexes.

5) Preoperative treatment with oral [diazepam](#) 10 mg results in a significant decrease in arterial oxygen tension and a significant decrease in alveolar-arterial oxygen tension difference in healthy males. These effects may be clinically important in patients with impaired cardiorespiratory reserve [118].

6) A 56-year old man with mild [obstructive lung disease](#), angina and [hypertension](#) received a 10 mg IV bolus of [diazepam](#) for anxiety during a [spermatocoele](#) repair. Within 2 to 5 minutes, the patient was unresponsive to verbal commands, apneic, and cyanotic. After initiation of [artificial respiration](#) and 15 minutes after the [diazepam](#) administration, the patient was awake and drowsy but responded to verbal stimuli. The patient recovered and was amnesiac about the entire procedure [119].

3.3.16] Other

3.3.16.A] Drug abuse

1) 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 [129]. Similar results have been reported [130].

3.3.16.B] Drug dependence

1) The likelihood of developing physical dependence and its severity are related to dose and duration of use. The development of dependence is more likely to occur with benzodiazepines such as [diazepam](#) with longer half-lives [131].

3.3.16.C] Drug withdrawal

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.D] Fatigue

1) Fatigue has been reported in patients using [diazepam](#) [84].

3.3.16.E] Withdrawal sign or symptom

1) [Diazepam](#) has a wide margin of safety; however, when using larger than normal doses over prolonged periods, psychological and physical dependence may develop [84]. Abrupt discontinuation has resulted in hallucinations and confusion [132] [133], grand mal seizures [134], restlessness, sleep disturbances, dizziness, apprehension, tremor, abdominal and muscle cramps, nausea, vomiting, [dysphoria](#), sweating, and headache [84] [135]. Gradual reduction in the dose is recommended [84].

2) Tolerance to [diazepam](#) was not observed when administered to chronically anxious outpatients in doses of 15 to 40 mg daily for 6 to 22 weeks. The duration of treatment appeared to be the most important determinant of withdrawal symptoms and patients treated for less than 8 months continuously had an incidence of withdrawal symptoms of 5%, whereas 43% of patients treated for 8 months or longer demonstrated clear withdrawal symptoms. No patient developed life-threatening withdrawal reactions, convulsions or psychotic reactions, and all reactions could be managed easily by tapering the dose of [diazepam](#) [136].

3) Benzodiazepine withdrawal symptoms have been reported in patients who received a short-acting benzodiazepine in substitution for a long-acting benzodiazepine [137]. One patient received [oxazepam](#) in substitution for [diazepam](#) and the other received [temazepam](#) in substitution for [flurazepam](#). Both patients received once daily doses of the shorter-acting agent resulting in withdrawal symptoms (insomnia, restlessness, dizziness, nausea, GI distress, irritability, blurred vision) which persisted for at least 1 month. It is suggested that substitution of a short-acting benzodiazepine in place of a long-acting benzodiazepine can be hazardous if a once daily dosing of the shorter-acting agent is initiated; this dose may not prevent emergence of withdrawal symptoms and the patients may require several daily doses. If withdrawal symptoms occur after substitution, reintroduction of the longer-acting benzodiazepine is recommended, followed by dosing reductions of 10% per day.

4) Tolerance was not observed to [diazepam](#) when administered to chronically anxious outpatients in doses of 15 to 40 milligrams daily for 6 to 22 weeks. The duration of treatment appeared to be the most important determinant of withdrawal symptoms and patients treated for less than 8 months continuously had an incidence of withdrawal symptoms of 5%, whereas 43% of patients treated for 8 months or longer demonstrated clear withdrawal symptoms. No patient developed life-threatening withdrawal reactions, convulsions or psychotic reactions, and all reactions could be managed easily by tapering the dose of [diazepam](#) [136].

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

A) **Teratogenicity/Effects in Pregnancy**

1) 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).

2) 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

3) Crosses Placenta: Yes

4) Clinical Management

a) In human and animal studies, major malformations and developmental abnormalities have been reported with [diazepam](#) use during pregnancy. Therefore, [diazepam](#) use in women of childbearing potential and during known pregnancy should be considered only when the benefit to the mother justifies the [risk to the fetus](#). The possibility of pregnancy should be considered in women of childbearing potential when initiating [diazepam](#) therapy. If [diazepam](#) is used during pregnancy or if the patient becomes pregnant while using the drug, she should be apprised of the potential harm to the fetus. Patients should also be advised to communicate with their healthcare professional about whether or not to discontinue [diazepam](#) if pregnancy occurs during therapy [84].

5) Literature Reports

a) 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 [380].

b) The use of benzodiazepine drugs during pregnancy has been associated with an increased risk of [congenital malformations](#) and other developmental abnormalities. Non-teratogenic risks may also be associated with benzodiazepine use during pregnancy. Neonatal flaccidity, respiratory and

feeding difficulties, and hypothermia have been reported in infants born to mothers who have been treated with benzodiazepines late in pregnancy. There may also be some risk of withdrawal symptoms in the infant during the postnatal period due to the mother receiving benzodiazepines regularly during late pregnancy [84].

c) In a meta-analysis reviewing outcomes of children born to mothers exposed to any benzodiazepine during their first trimester, mixed results were found. When they considered only cohort studies, no significant association between benzodiazepine use and either major malformations or oral cleft malformations were seen. However, data from case control studies showed a small but significant increased risk for major malformations ($p=0.008$) and for [cleft lip](#) ($p=0.01$) [381].

d) Severe [dysmorphism](#), malformations, intrauterine and extrauterine [growth retardation](#), and central nervous system dysfunction have been described in 7 infants born of mothers who used benzodiazepines during pregnancy [382].

e) Administration of benzodiazepines to women prior to delivery may produce signs of poisoning in the neonate (ie, difficulties in sucking and respiratory arrest requiring assisted ventilation) within the first hours or days after delivery. In neonates, a condition, called "[floppy infant syndrome](#)", may occur, following maternal [diazepam](#) consumption, and is characterized by hypotonia that may last over several days [383] [384].

f) A case report described [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 [385]. In another case report, neonatal drug withdrawal in an infant whose mother's [epilepsy](#) was being treated with [diazepam](#) was accompanied by the syndrome of [inappropriate secretion of antidiuretic hormone](#) (SIADH). Because of poor feeding, intravenous infusion of a 5% glucose solution was instituted on day 1 after birth. Oliguria was recognized (urine output less than 0.5 mL/kg/hr) on day 1, and fluid was then restricted to 65 mL/kg/day and a diuretic given. After day 3, urine output increased and [urine osmolality](#) decreased. Oliguria did not recur. At 60 days, there was no evidence of abnormalities of the brain; development at 6 months of age was normal [386].

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. Monitor infant for side effects.

3) Micromedex Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

4) Clinical Management

a) [Diazepam](#) has been shown to be excreted in breast milk. Therefore, breastfeeding is not recommended in nursing mothers who are receiving [diazepam](#) [84].

5) Literature Reports

a) In a study conducted to determine the serum concentrations of benzodiazepines and antidepressants in nursing infants, of 35 infants tested whose mothers were taking antidepressants or benzodiazepines while breastfeeding, 74% had serum medication levels below the laboratory limit of detection. Twenty-six percent of the infants, with detectable serum medication levels, were also exposed to the medication during pregnancy [389].

b) Milk and plasma concentrations of diazepam, N-desmethyldiazepam, temazepam, and oxazepam in the breast milk of a 22-year-old mother were observed during withdrawal from diazepam and oxazepam combination therapy. Milk:plasma ratios of diazepam and N-desmethyldiazepam were 0.2 and 0.13, respectively, and the calculated infant dose was 4.7% of that ingested by the mother. While serum concentrations of diazepam were not detected in the infant, low levels of the metabolite and concomitant temazepam were present. No adverse effects were noted in this infant [390].

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.14-0.21 [425]

b) Active Metabolites

1) N-desmethyldiazepam, N-methyloxazepam (temazepam) [424]

a) Milk to Maternal Plasma Ratio

1) 0.13 [390]

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 [255]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [256]. 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 [223].

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 [254].

3.5.1.B] [Amitriptyline](#)

- 1) Interaction Effect: psychomotor deficits (decreased reaction time, decreased vigilance)
- 2) Summary: A controlled study observed that coadministration of [diazepam](#) with [amitriptyline](#) resulted in additive deficits in several psychomotor tests [185]. The potential interaction between [diazepam](#) and [amitriptyline](#) was studied in four depressed patients receiving 75 to 150 mg daily of [amitriptyline](#) and 10 to 15 mg daily of [diazepam](#) [186]. Researchers were unable to demonstrate any change in blood levels of [amitriptyline](#) or [nortriptyline](#). Additional controlled studies or case reports are necessary to determine the degree of impairment resulting from coadministration of these two agents.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: If coadministration of [amitriptyline](#) with [diazepam](#) is necessary, patients should be warned that they may experience additive [psychomotor impairment](#) that may affect driving or other tasks requiring complex motor skills.
- 7) Probable Mechanism: additive psychomotor deficits
- 8) Literature Reports

a) In a controlled study of performance of 90 healthy volunteers, the effects of [fluoxetine](#), [amitriptyline](#), or placebo on [diazepam](#) were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. [Fluoxetine](#) alone did not affect performance, but when [fluoxetine](#) was added to [diazepam](#), there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For [amitriptyline](#) alone and during coadministration with [diazepam](#) significant impairment was observed. On most tests, the combination of [amitriptyline](#) and [diazepam](#) resulted in additive effects. The authors concluded that the combination of [diazepam](#) and an antidepressant may increase an individual's risk during driving and while performing other complex tasks [184].

3.5.1.C] [Amobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.D) [Amprenavir](#)

- 1)) Interaction Effect: an increased risk of [diazepam](#) toxicity (excessive sedation, confusion)
- 2)) Summary: Serum concentrations of [diazepam](#) may be elevated by the concurrent administration of [amprenavir](#). Currently no interaction study has been conducted. [Amprenavir](#) and [diazepam](#) are both metabolized by cytochrome P450 3A4 enzymes, in addition to [amprenavir](#) inhibiting CYP3A4. Competition for metabolism and/or inhibition of metabolism could result in an increased plasma concentration of [diazepam](#) [171].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Caution should be exercised if [diazepam](#) and [amprenavir](#) are administered concurrently. The patient should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#).
- 7)) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [diazepam](#) metabolism by [amprenavir](#)

3.5.1.E) [Anileridine](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.F] Aprobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.G] Armodafinil

- 1) Interaction Effect: increased [diazepam](#) exposure
- 2) Summary: Administration of armodafinil (R-enantiomer of [modafinil](#)) may cause moderate inhibition of CYP2C19 isozyme activity. Although not studied with [diazepam](#), a CYP2C19 substrate, concurrent administration of a single 400-mg dose of armodafinil with a 40-mg dose of [omeprazole](#), also a CYP2C19 substrate, led to an approximately 40% increase in systemic exposure of [omeprazole](#). Therefore, use caution when armodafinil and [diazepam](#) are used concurrently. Dose reductions of [diazepam](#) may be necessary [183]. Also, monitor patients for increased [diazepam](#) adverse events (excessive sedation, confusion).
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the coadministration of armodafinil and [diazepam](#) as this may result in increased [diazepam](#) exposure. Dose reductions of [diazepam](#) may be necessary [183]. Monitor patients for increased [diazepam](#) adverse events (excessive sedation, confusion).
- 7) Probable Mechanism: inhibition of CYP2C19-mediated [diazepam](#) metabolism

3.5.1.H] 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 [264].

- 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 [264].
- 7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.I] [Butabarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.J] [Butalbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.K] [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 [214] [215]. 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 [214] [215]. 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.L] [Carisoprodol](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7)) Probable Mechanism: CNS depression

3.5.1.M] [Chloral Hydrate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: [Chloral hydrate](#), with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [232]. 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.N] [Chlorzoxazone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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] [Cimetidine](#)

- 1) Interaction Effect: [diazepam](#) toxicity (CNS depression)
- 2) Summary: [Cimetidine](#) decreases the clearance of benzodiazepines that are metabolized by hydroxylation or dealkylation (eg, [diazepam](#), [chlordiazepoxide](#), [clorazepate](#), [flurazepam](#), [prazepam](#), [halazepam](#), [alprazolam](#), [triazolam](#), [midazolam](#), [quazepam](#), [estazolam](#), bromazepam) [272] [273] [274] [275]. Specifically, [cimetidine](#) causes [diazepam](#) demethylation (and subsequent desmethyldiazepam hydroxylation) to be slowed [276]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [277] [278]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, nitrazepam, [clonazepam](#)) [279] [280]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [281] [282] [283] [284].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce benzodiazepine dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: decreased [diazepam](#) metabolism
- 8) Literature Reports

a) Some studies evaluated the clinical significance of the cimetidine-diazepam interaction. Patients receiving long term treatment with [diazepam](#) were given [cimetidine](#) concurrently. Although [diazepam](#) clearance was inhibited during concomitant administration, clinical signs and symptoms such as reaction-time and drowsiness did not change significantly. In contrast, [269] documented pronounced sedation when [cimetidine](#) and [diazepam](#) were given concurrently to patients not previously receiving [diazepam](#). Diazepam is metabolized by the cytochrome P450 enzyme system. Cimetidine was reported to inhibit individual enzymes in the P450 system in studies of combined [cimetidine](#) and [diazepam](#) in vitro and in vivo both in animals and humans [270]. The demethylation of [diazepam](#) and subsequent hydroxylation of its main metabolite (desmethyldiazepam) were slowed by concurrent administration of [cimetidine](#) [271].

3.5.1.P] [Clarithromycin](#)

- 1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [243] [244] [245] [246].
- 3) Severity: moderate
- 4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.

7) Probable Mechanism: decreased hepatic metabolism; decreased [diazepam](#) clearance

8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 ng/mL [240].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg TID for 3 days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [241].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following 5 days of [erythromycin](#) therapy versus placebo [242].

3.5.1.Q] Cobicistat

1) Interaction Effect: increased [diazepam](#) exposure

2) Summary: Coadministration of cobicistat (a strong CYP3A4 inhibitor) and [diazepam](#) (a CYP3A4 substrate) may result in increased [diazepam](#) plasma concentrations and an increased risk of toxicity. If concurrent use is required, dose reductions of [diazepam](#) and clinical monitoring is recommended [360].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of cobicistat (a strong CYP3A4 inhibitor) and [diazepam](#) (a CYP3A4 substrate) may result in increased [diazepam](#) plasma concentrations and an increased risk of toxicity. If concurrent use is required, dose reductions of [diazepam](#) and clinical monitoring is recommended [360].

7) Probable Mechanism: inhibition of CYP3A4-mediated [diazepam](#) metabolism by cobicistat

3.5.1.R] Codeine

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].

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 [254].

3.5.1.S] [Dalfopristin](#)

- 1) Interaction Effect: an increased risk of [diazepam](#) toxicity (excessive sedation, confusion)
- 2) Summary: The concurrent administration of [quinupristin/dalfopristin](#) and [diazepam](#) may result in increased levels of [diazepam](#). [Quinupristin/dalfopristin](#) is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and [diazepam](#) is a CYP3A4 substrate [266].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [quinupristin/dalfopristin](#) and [diazepam](#) should be undertaken with caution. Patients should be monitored for signs of excessive central nervous system depression. Doses of [diazepam](#) may need to be reduced.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [diazepam](#) metabolism

3.5.1.T] [Dantrolene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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.U] [Darunavir](#)

- 1) Interaction Effect: increased sedative or hypnotic exposure
- 2) Summary: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with sedatives or hypnotics metabolized by CYP3A, as increased plasma concentrations of CYP3A-metabolized sedatives or hypnotics may result. Consider titration and a lower dose of CYP3A-metabolized sedatives or hypnotics with concurrent use. Monitor for adverse reactions and increased or prolonged sedative or hypnotic effects if coadministered [172].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with sedatives or hypnotics metabolized by CYP3A, as increased plasma concentrations of CYP3A-metabolized sedatives or hypnotics may result. Consider titration and a lower dose of CYP3A-metabolized sedatives or hypnotics with concurrent use. Monitor for adverse reactions and increased or prolonged sedative or hypnotic effects if coadministered [172].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by [darunavir](#)

3.5.1.V] [Desogestrel](#)

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.W] [Dienogest](#)

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive
- 8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of diazepam 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in diazepam clearance or protein binding between the two groups. However, apparent elimination half-life of diazepam was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [343]. A similar interaction would also be expected with alprazolam, halazepam, prazepam, clorazepate, flurazepam, and triazolam which are oxidatively metabolized in the liver [344].

3.5.1.X] Digoxin

- 1) Interaction Effect: digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
- 2) Summary: Concomitant administration of alprazolam or diazepam and digoxin has been reported to increase digoxin concentrations (5 to 100%). Increased monitoring of digoxin levels are suggested when either adding or deleting alprazolam or diazepam therapy to patients stabilized on digoxin therapy [180] [181] [182].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for signs of digoxin intoxication (eg, nausea, vomiting, diarrhea, persistent headache, confusion, fainting, visual disturbances). If symptoms are present, obtain a digoxin level and reduce dose accordingly.
- 7) Probable Mechanism: unknown

3.5.1.Y] Disulfiram

- 1) Interaction Effect: an increased risk of central nervous system depression
- 2) Summary: Disulfiram (500 mg daily for two weeks) decreased diazepam clearance by 41% and increased elimination half-life by 37%. Disulfiram does not affect the disposition of oxazepam, lorazepam, and possibly temazepam [239].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable

6j) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce [diazepam](#) dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#)).

7j) Probable Mechanism: decreased [diazepam](#) metabolism

8j) Literature Reports

a) Concomitant [disulfiram](#) and benzodiazepine therapy may potentiate the sedative effects of the benzodiazepine. The metabolic clearance of various benzodiazepines when given concurrently with [disulfiram](#) was studied. Determinations of plasma [chlordiazepoxide](#) concentrations showed that the parent compound and desmethyl metabolite had a decreased plasma clearance in both healthy and alcoholic patients. The plasma clearance of [diazepam](#) decreased in both healthy and alcoholic patients by 41%. There was a corresponding decrease in the active N-desmethyl metabolites of both drugs. [Disulfiram](#) increased the half-life of [chlordiazepoxide](#) by 84% and [diazepam](#) by 37%. The disposition of [oxazepam](#) was not altered significantly by [disulfiram](#), but the half-life was increased by 17%. [Oxazepam](#) may be the drug of choice in patients on [disulfiram](#) who require benzodiazepine therapy [238].

3.5.1.Z] Dong Quai

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

2j) Summary: Dong quai extract inhibited metabolism of [diazepam](#) and increased its muscle relaxant effect in rats [349]. 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](#) [349]. 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

a) *Angelica dahurica* (dong quai) extract 1 gram/kilogram orally increased the maximum concentration of oral [diazepam](#), yet did not alter pharmacokinetics of intravenous (IV) [diazepam](#) in rats. [Diazepam](#) 5 milligrams/kilogram (mg/kg) was administered orally to rats alone, and one hour after dong quai extract. When administered alone, only the maximum concentration (C_{max}) of [diazepam](#) could be calculated, as the plasma concentration of [diazepam](#) was undetectable at all sample time points except for 2 hours. After dong quai, [diazepam](#) C_{max} increased from 23.0 +/- 12.4 nanograms/milliliter (ng/mL) to 92.1 +/- 50.3 ng/mL (p less than 0.05). [Diazepam](#) pharmacokinetics were not significantly changed by dong quai when [diazepam](#) was administered intravenously. [Diazepam](#) is metabolized by CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation. Dong quai extract inhibited all of these isoenzymes [348].

b) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly increased the muscle relaxant effect of [diazepam](#) (5 mg/kg IV) in rats. Duration of rotarod disruption was increased with high-dose oral dong quai (1 gram/kg) versus [diazepam](#) alone (p less than 0.05). Low-dose oral dong quai (0.3 grams/kg) had no effect on rotarod performance when administered with [diazepam](#) 5 mg/kg IV. Dong quai administered alone had no effect on rotarod performance [348].

3.5.1.AA] [Drospirenone](#)

- 1)** Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)
- 2)** Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3)** Severity: minor
- 4)** Onset: delayed
- 5)** Substantiation: probable
- 6)** Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.
- 7)** Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive
- 8)** Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.AB] [Erythromycin](#)

- 1)** Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2)** Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [331] [332] [333] [334].

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 ng/mL [328].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg TID for 3 days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [329].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following 5 days of [erythromycin](#) therapy versus placebo [330].

3.5.1.AC] [Eslicarbazepine Acetate](#)

- 1) Interaction Effect: increased exposure of CYP2C19 substrates
- 2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP2C19 inhibitor) with a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate [267]. If coadministering, use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP2C19 inhibitor) with a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate [267]. If coadministering, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism by eslicarbazepine acetate

3.5.1.AD] [Esomeprazole](#)

- 1) Interaction Effect: increased exposure of [diazepam](#)
- 2) Summary: Use caution with the concurrent administration of [diazepam](#) (a CYP2C19 substrate) and [esomeprazole](#) (a CYP2C19 inhibitor). Coadministration of [diazepam](#) with [esomeprazole](#) 30 mg resulted in a 45% decrease in the clearance of [diazepam](#) [152], which may potentially cause [diazepam](#) toxicities.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Use caution with the concurrent administration of [diazepam](#) (a CYP2C19 substrate) and [esomeprazole](#) (a CYP2C19 inhibitor) [152], as coadministration may potentially cause [diazepam](#) toxicities.

7) Probable Mechanism: inhibition of CYP2C19-mediated [diazepam](#) metabolism by [esomeprazole](#)

3.5.1.AE] [Estradiol](#) Cypionate

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.AF] [Estradiol](#) Valerate

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the

possibility of increased clinical effects although a direct relation between diazepam's plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of diazepam 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in diazepam clearance or protein binding between the two groups. However, apparent elimination half-life of diazepam was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [343]. A similar interaction would also be expected with alprazolam, halazepam, prazepam, clorazepate, flurazepam, and triazolam which are oxidatively metabolized in the liver [344].

3.5.1.AG| Ethchlorvynol

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [235].

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.AH| Ethinyl Estradiol

1) Interaction Effect: diazepam toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of diazepam, alprazolam, triazolam and chlordiazepoxide. Combination contraceptives may increase the effect of diazepam on psychomotor performance [345] [346] [347]. Therefore, diazepam dosage reduction may be necessary in patients receiving both diazepam and oral contraceptive steroids. Patients should be monitored for the

possibility of increased clinical effects although a direct relation between diazepam's plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of diazepam 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in diazepam clearance or protein binding between the two groups. However, apparent elimination half-life of diazepam was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [343]. A similar interaction would also be expected with alprazolam, halazepam, prazepam, clorazepate, flurazepam, and triazolam which are oxidatively metabolized in the liver [344].

3.5.1.AII Ethynodiol Diacetate

1) Interaction Effect: diazepam toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of diazepam, alprazolam, triazolam and chlordiazepoxide. Combination contraceptives may increase the effect of diazepam on psychomotor performance [345] [346] [347]. Therefore, diazepam dosage reduction may be necessary in patients receiving both diazepam and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between diazepam's plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more

than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.AJ] [Etonogestrel](#)

- 1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam](#)'s plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive
- 8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b)) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.AK] Etravirine

- 1)) Interaction Effect: increased [diazepam](#) plasma concentrations
- 2)) Summary: Concomitant use of etravirine and [diazepam](#) may increase plasma concentrations of [diazepam](#) due to inhibition of CYP3A4-mediated [diazepam](#) metabolism by etravirine. A decrease in [diazepam](#) dose may be necessary [358].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of etravirine and [diazepam](#) may result in significant increases in [diazepam](#) plasma concentrations due to inhibition of CYP3A4-mediated [diazepam](#) metabolism by etravirine. If concomitant use is required, dose reductions of [diazepam](#) may be necessary [358].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated [diazepam](#) metabolism by etravirine

3.5.1.AL] Evening Primrose

- 1)) Interaction Effect: reduced anticonvulsant effectiveness
- 2)) Summary: Evening primrose oil contains gamolenic acid (GLA), which may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [168]. Evening primrose oil is contraindicated in patients with [epilepsy](#) [169] [170].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants. Evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [168].
- 7)) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.AM] [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 [222]. 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](#) [223]. 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 [222].
- 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 [222].

7J) Probable Mechanism: additive CNS depression

3.5.1.AN] [Flumazenil](#)

1J) Interaction Effect: precipitation of seizures

2J) Summary: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [167].

3J) Severity: contraindicated

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [167].

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

3.5.1.AO] [Fluoxetine](#)

1J) Interaction Effect: higher serum concentrations of [diazepam](#)

2J) Summary: During coadministration of [fluoxetine](#) with [diazepam](#), the [fluoxetine](#) area under the concentration-time curve (AUC) was increased, but this was not associated with increased impairment [209]. Conversely, a controlled study observed significant decreases in psychomotor performance when [diazepam](#) was added to [fluoxetine](#) [210]. The metabolism of [diazepam](#) is mediated by several P450 enzymes which may be inhibited by [fluoxetine](#) [211] [212] [213]. Further case reports or controlled studies are necessary to appropriately define the pharmacokinetic effects as well as the degree of [psychomotor impairment](#) resulting from coadministration of these two agents.

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Although dose adjustments are thought not to be necessary when [fluoxetine](#) and [diazepam](#) are given concomitantly, monitor patients for signs and symptoms of excessive [diazepam](#) concentrations (sedation, dizziness, ataxia, decreased cognition or motor performance). In some patients, such as the elderly, it may be safer to give a lower dose of [diazepam](#) during combination therapy.

7J) Probable Mechanism: inhibition of the hepatic P450 metabolism of [diazepam](#)

8J) Literature Reports

aJ) Coadministration of [fluoxetine](#) and [diazepam](#) resulted in prolonged half-life, reduced plasma clearance, and increased AUC for [diazepam](#). Oral [diazepam](#) 10 mg was given alone, after a single dose of oral [fluoxetine](#) 60 mg, and after 8 daily doses of [fluoxetine](#) 60 mg. Psychometric data demonstrated no effect of [fluoxetine](#) on the psychomotor response to [diazepam](#). Thus, although [fluoxetine](#) decreases the clearance of [diazepam](#), this does not appear to be of clinical relevance and dosing adjustments are not required during combined therapy [202].

bJ) Combined therapy with [diazepam](#) and [fluoxetine](#) caused an increase in the half-life of the metabolite desmethyldiazepam, but this did not appear to be clinically significant. [Diazepam](#) had no effect on the disposition of [fluoxetine](#) or norfluoxetine [203].

c) To date, in-vitro studies have found that [diazepam](#) demethylation occurs via P450 1A2, 3A4, 2C9, and 2C19. Evidence with drugs known to be metabolized by these enzymes suggests that [fluoxetine](#) strongly inhibits 2C9, moderately inhibits 2C19 and 3A4, and has no effect on 1A2 [204] [205] [206].

d) In a controlled study of performance of 90 healthy volunteers, the effects of [fluoxetine](#), [amitriptyline](#), or placebo with [diazepam](#) were studied. Volunteers received one of six treatment combinations, and were given performance tests including a critical tracking test, divided attention test, visual search task, memory test, and vigilance test. [Fluoxetine](#) alone did not affect performance, but when [fluoxetine](#) was added to [diazepam](#), there was a significant increase in the divided attention tracking error and significant impairment on the vigilance test. For [amitriptyline](#) alone and during coadministration with [diazepam](#), significant impairment was observed. On most tests, the combination of [amitriptyline](#) and [diazepam](#) resulted in additive effects. The authors concluded that the combination of [diazepam](#) and an antidepressant may increase an individual's risk during driving and while performing other complex tasks [207].

e) A case was reported in which an 83-year old man developed [delirium](#) after the addition of [fluoxetine](#) and [diazepam](#) to a regimen of [warfarin](#), [lisinopril](#), [furosemide](#), potassium, [digoxin](#), and [acetaminophen](#). The patient was given [fluoxetine](#) 20 mg per day and [diazepam](#) 2.5 mg three to four times per day for symptoms of depression, anxiety, and insomnia. The patient then developed symptoms of drug [delirium](#), including confusion, incoherence, and irrational speaking. The patient also developed an increased [international normalized ratio \(INR\)](#), after which [fluoxetine](#) was discontinued. The patient presented to the hospital with left-sided weakness and later died from complications of a large interparenchymal hemorrhage. The authors proposed that the addition of [fluoxetine](#) to the patient's regimen resulted in increased serum levels of both [warfarin](#) and [diazepam](#), resulting in drug-induced [delirium](#) and loss of anticoagulant control [208].

3.5.1.AP] [Fluvoxamine](#)

1) Interaction Effect: [diazepam](#) and N-desmethyldiazepam accumulation

2) Summary: Coadministration of [fluvoxamine](#) 150 mg daily with a single oral dose of [diazepam](#) 10 mg resulted in a 65% decrease in clearance of [diazepam](#). The clearance of [diazepam's](#) primary active metabolite, N-desmethyldiazepam, is reduced to immeasurable levels. This effect may be more pronounced with increasing doses of [fluvoxamine](#) [217].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Diazepam](#) and [fluvoxamine](#) should not be taken concurrently due to the possibility of significant [diazepam](#) accumulation. Consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) and monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance).

7) Probable Mechanism: reduced [diazepam](#) clearance

3.5.1.AQ] [Fosamprenavir](#)

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

2) Summary: Plasma concentrations of [diazepam](#) may be elevated by the concurrent administration of [fosamprenavir](#). [Amprenavir](#), the active metabolite of [fosamprenavir](#), and [diazepam](#) are both metabolized by CYP3A4 isoenzymes, and [amprenavir](#) is also an inhibitor of CYP3A4. Competition for metabolism

and/or inhibition of metabolism could result in an increased plasma concentration of [diazepam](#). Although clinical significance is unknown, a decrease in [diazepam](#) dosing may be warranted [247].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution should be exercised if [diazepam](#) and [fosamprenavir](#) are administered concurrently. Monitor the patient for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#). A decrease in [diazepam](#) dose may be necessary [247].

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

3.5.1.AR] Fosphenytoin

1) Interaction Effect: alterations in serum [phenytoin](#) concentrations

2) Summary: Use caution with the concomitant administration of [phenytoin](#) and [diazepam](#), as [phenytoin](#) levels may be decreased [224] [225] or increased [226]. Consider obtaining [phenytoin](#) serum concentrations if concomitant administration is necessary. [Phenytoin](#) dose adjustments may be required, especially with the addition or withdrawal of [diazepam](#) [224] [225].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with the concomitant administration of [phenytoin](#) and [diazepam](#), as [phenytoin](#) levels may be decreased [224] [225] or increased [226]. Consider obtaining [phenytoin](#) serum concentrations if concomitant administration is necessary. [Phenytoin](#) dose adjustments may be required, especially with the addition or withdrawal of [diazepam](#) [224] [225].

7) Probable Mechanism: unknown

8) Literature Reports

a) [Phenytoin](#) toxicity occurred in a 44-year-old man who was given concomitant [diazepam](#) therapy. The patient complained of headache, [nystagmus](#), [diplopia](#), and ataxia and was admitted to the hospital. Aside from his long-standing seizure disorder, his past medical history was unremarkable. His antiepileptic regimen of [phenytoin](#), [phenobarbital](#), and [lamotrigine](#) had been unchanged for almost 5 months. Two weeks prior to admission his total [phenytoin](#) serum concentration was 8 mcg/mL. He was prescribed [amoxicillin](#) and [diazepam](#) 2 days prior to his hospital admission. His serum [phenytoin](#) concentration was 37 mcg/mL in the hospital. [Diazepam](#) and [phenytoin](#) were discontinued and the symptoms resolved [226].

3.5.1.AS] 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 [149]. 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.AT] Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness

2) Summary: In a case report, 2 patients with [epilepsy](#) previously well controlled by [valproate](#) sodium developed a recurrence of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn [321]. An infant developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds [322]. The compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as in leaves, the ginkgo component from which commercially available extracts are derived [323]. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridoxine is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known seizure disorders).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

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

8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine levels. The serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for the tonic/[clonic convulsions](#) and loss of consciousness observed. They further observed that infants are particularly vulnerable [318].

b) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of Ginkgo biloba leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was detected in medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested [319].

c) Seizures recurred in 2 patients, both with [epilepsy](#) that was well controlled prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without changing [anticonvulsant therapy](#)) after discontinuing Gb [320].

3.5.1.AU] [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 [237].
- 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 [237].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AV] [Hydromorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.AW] [Isoniazid](#)

- 1) Interaction Effect: an increased risk of benzodiazepine toxicity (sedation, [respiratory depression](#))

2) Summary: Concomitant [diazepam](#) and [isoniazid](#) therapy has been reported to result in a prolongation of [diazepam's](#) plasma half-life and a reduction in its clearance. The decrease in metabolism of [diazepam](#) is thought to be due to the ability of [isoniazid](#) to inhibit hepatic microsomal enzymes [228] [229]. Some patients may require a reduction in [diazepam](#) dosage with concurrent [isoniazid](#) therapy.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving [isoniazid](#) and [diazepam](#) for signs of benzodiazepine toxicity, including [respiratory depression](#), somnolence, and sedation.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [diazepam](#) metabolism

3.5.1.AX] [Itraconazole](#)

1) Interaction Effect: increased [diazepam](#) concentrations and potential [diazepam](#) toxicity (excessive sedation and prolonged hypnotic effects)

2) Summary: Coadministration of [itraconazole](#) and [diazepam](#) may increase exposure to [diazepam](#). Azole antifungals are thought to inhibit the metabolism of drugs cleared by the cytochrome P450 3A subfamily of enzymes and, possibly, the P450 2C subfamily [139] [140]. If concurrent use is required, consider reducing the dose of [diazepam](#) and monitor for increased [diazepam](#) toxicity (excessive sedation and prolonged hypnotic effects) [141].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [itraconazole](#) and [diazepam](#) may cause elevated [diazepam](#) concentrations and possibly depressed psychomotor function. If concurrent use is required, consider reducing the dose of [diazepam](#) and monitor for increased [diazepam](#) toxicity (excessive sedation and prolonged hypnotic effects).

7) Probable Mechanism: inhibition of the P450 3A4 enzyme system-mediated [diazepam](#) metabolism by [itraconazole](#)

3.5.1.AY] [Ivacaftor](#)

1) Interaction Effect: increased [diazepam](#) exposure

2) Summary: [Diazepam](#) is CYP3A4 substrate. Although not specifically studied with [diazepam](#), the concomitant administration of ivacaftor, a CYP3A inhibitor, and [midazolam](#), also a CYP3A4 substrate, increased [midazolam](#) AUC by 1.5-fold. As a similar reaction can be expected with [diazepam](#), caution and monitoring for benzodiazepine-related side effects are advised if these agents are coadministered [342].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution if [diazepam](#) and ivacaftor are coadministered as this may result in increased [diazepam](#) exposure. Monitor for benzodiazepine-related side effects [342].

7) Probable Mechanism: inhibition of CYP3A4-mediated [diazepam](#) metabolism

3.5.1.AZ] [Josamycin](#)

1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)

2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [260] [261] [262] [263].

3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in one hour by intravenous [erythromycin](#) 400 mg. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 mg/mL [257].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg three times daily for three days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from four to six hours, and decreased the volume of distribution [258].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following five days of [erythromycin](#) therapy versus placebo [259].

3.5.1.BA] 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](#) [296]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [297].
- 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 [295].

3.5.1.BB] Ketorolac

- 1) Interaction Effect: reduced anticonvulsant effectiveness

- 2) Summary: The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures. Sporadic cases of seizures have been reported in patients who received ketorolac together with an antiepileptic drug [150].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution when prescribing ketorolac to patients who take anticonvulsants. The concomitant use of ketorolac and an anticonvulsant (such as [phenytoin](#) or [carbamazepine](#)) may cause an increased risk of seizures [150].
- 7) Probable Mechanism: unknown

3.5.1.BC] [Levonorgestrel](#)

- 1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive
- 8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.BD] [Levorphanol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.BE] [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 [233] and use with caution [234].
- 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 [233] and use with caution [234].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BF] [Magnolia](#)

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [303] [304] [305]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [306]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [307]. 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 [298].

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 [299].

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 [300].

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) [301].

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 [302].

3.5.1.BG| 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](#) [339] [340] [341] 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](#) [339] [340] [341] 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.BH| Medroxyprogesterone Acetate

- 1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive
- 8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#)

metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.BI] Meperidine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.BJ] Mephesisin

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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.BK] Mephobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.BL] [Meprobamate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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.BM] [Mestranol](#)

- 1)) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)
- 2)) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3)) Severity: minor
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.
- 7)) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive
- 8)) Literature Reports

a)) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the

control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b)) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [343]. A similar interaction would also be expected with alprazolam, halazepam, prazepam, clorazepate, flurazepam, and triazolam which are oxidatively metabolized in the liver [344].

3.5.1.BN] Metaxalone

- 1)) Interaction Effect: additive respiratory depression
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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.BO] 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 [253].
- 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 [253].
- 7)) Probable Mechanism: additive CNS depression effects

3.5.1.BP] Methocarbamol

- 1)) Interaction Effect: additive respiratory depression
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [354] [355] [356] [357].
- 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.BQ] [Methohexital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.BR] [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 [265].
- 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 [265].
- 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 [265].

3.5.1.BS] Modafinil

- 1) Interaction Effect: increased plasma concentrations of [diazepam](#)
- 2) Summary: Coadministration of [modafinil](#) with [diazepam](#) may lead to prolonged elimination of [diazepam](#) resulting in increased plasma concentrations. Due to the inhibition of CYP2C19 by [modafinil](#), doses of [diazepam](#) may need to be reduced to limit toxicity [227].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The patient should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#). Doses of [diazepam](#) may need to be reduced to limit toxicity.
- 7) Probable Mechanism: reversible inhibition by [modafinil](#) of cytochrome P450 2C19 mediated [diazepam](#) metabolism

3.5.1.BT] Morphine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.BU] Morphine Sulfate Liposome

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.BV] [Norelgestromin](#)

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.BW] [Norethindrone](#)

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in

patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of [diazepam](#). Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of [diazepam](#) 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in [diazepam](#) clearance or protein binding between the two groups. However, apparent elimination half-life of [diazepam](#) was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with [diazepam](#) plus contraceptives compared with [diazepam](#) alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of [diazepam](#), it is likely that experience with oral administration of [diazepam](#) would be similar since [diazepam](#) is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.BX] [Norgestimate](#)

1) Interaction Effect: [diazepam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may decrease the metabolism of [diazepam](#), [alprazolam](#), [triazolam](#) and [chlordiazepoxide](#). Combination contraceptives may increase the effect of [diazepam](#) on psychomotor performance [345] [346] [347]. Therefore, [diazepam](#) dosage reduction may be necessary in patients receiving both [diazepam](#) and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between [diazepam's](#) plasma concentration and its clinical effectiveness has not clearly been established [343].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and [diazepam](#) for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of oxidative [diazepam](#) metabolism by the contraceptive

8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair [diazepam](#) clearance and significantly increase the elimination half-life of

diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of **diazepam** 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in **diazepam** clearance or protein binding between the two groups. However, apparent elimination half-life of **diazepam** was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with **diazepam** plus contraceptives compared with **diazepam** alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of **diazepam**, it is likely that experience with oral administration of **diazepam** would be similar since **diazepam** is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the **diazepam**/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated **diazepam** metabolism by the estrogen. This would subsequently reduce the oxidation of **diazepam** in the liver [343]. A similar interaction would also be expected with **alprazolam**, **halazepam**, **prazepam**, **clorazepate**, **flurazepam**, and **triazolam** which are oxidatively metabolized in the liver [344].

3.5.1.BY] Norgestrel

- 1) Interaction Effect: **diazepam** toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may decrease the metabolism of **diazepam**, **alprazolam**, **triazolam** and **chlordiazepoxide**. Combination contraceptives may increase the effect of **diazepam** on psychomotor performance [345] [346] [347]. Therefore, **diazepam** dosage reduction may be necessary in patients receiving both **diazepam** and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between **diazepam**'s plasma concentration and its clinical effectiveness has not clearly been established [343].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and **diazepam** for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of oxidative **diazepam** metabolism by the contraceptive
- 8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair **diazepam** clearance and significantly increase the elimination half-life of **diazepam**. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of **diazepam** 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in **diazepam** clearance or protein binding between the two groups. However, apparent elimination half-life of **diazepam** was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with **diazepam** plus contraceptives compared with **diazepam** alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [343]. Although these results refer only to intravenous administration of **diazepam**, it is likely that experience with oral administration of **diazepam** would be similar since **diazepam** is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the [diazepam](#)/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated [diazepam](#) metabolism by the estrogen. This would subsequently reduce the oxidation of [diazepam](#) in the liver [343]. A similar interaction would also be expected with [alprazolam](#), [halazepam](#), [prazepam](#), [clorazepate](#), [flurazepam](#), and [triazolam](#) which are oxidatively metabolized in the liver [344].

3.5.1.BZ] [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 [216].
- 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 [216].
- 7) Probable Mechanism: additive CNS depression

3.5.1.CA] [Omeprazole](#)

- 1) Interaction Effect: enhanced and prolonged [diazepam](#) effects
- 2) Summary: Concurrent use of [diazepam](#) and [omeprazole](#) has been reported to slow [diazepam](#) metabolism and delay its elimination, thereby resulting in enhanced and prolonged benzodiazepine effects [312] [313] [314]. One study indicated that decreased [diazepam](#) clearance occurred in almost one-half of patients who were fast metabolizers of [omeprazole](#) but the combination had little significance in slow metabolizers of [omeprazole](#) [315].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of excessive benzodiazepine effects (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce [diazepam](#) dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: inhibition by [omeprazole](#) and metabolites of [diazepam](#) metabolism
- 8) Literature Reports

a) In a double blind, crossover study, the addition of [omeprazole](#) in patients taking [diazepam](#) resulted in a 25% to 50% reduction in [diazepam](#) clearance. This interaction occurred in about 40% of patients who were fast metabolizers of [omeprazole](#). In slow metabolizers, this interaction was of little significance [308].

b) Concomitant administration of [diazepam](#) and [omeprazole](#) resulted in a 130% increase in mean elimination half-life of [diazepam](#) and subsequent increases in plasma [diazepam](#) concentrations [309].

c) Diazepam is metabolized by the cytochrome P450 enzyme system. Omeprazole was reported to inhibit individual enzymes in the P450 system in studies of combined [omeprazole](#) and [diazepam](#) in vitro and in vivo both in animals and humans [310]. The demethylation of [diazepam](#) and

subsequent hydroxylation of its main metabolite (desmethyldiazepam) were slowed by concurrent administration of [omeprazole](#).

d) Human liver microsomes were used to study the metabolism of [diazepam](#) to its two major metabolites nordiazepam (NDZ) and 3-hydroxydiazepam (3-HDZ). In addition, inhibition of these two pathways by [omeprazole](#) and [omeprazole](#) sulphone was studied. [Omeprazole](#) sulphone inhibited both pathways comparably; however, NDZ pathway was less susceptible to [omeprazole](#) inhibition [311].

3.5.1.CB| [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 [138].
- 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 [138].
- 7) Probable Mechanism: unknown

3.5.1.CC| [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 [337] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [338].
- 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 [337] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [338].
- 7) Probable Mechanism: additive effects

3.5.1.CD| [Oxymorphone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.CE] 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 [285]. 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 [285]. 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 [285].

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 [325]. 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 [326]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [327].

3.5.1.CF] [Pentobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.CG] [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 [236].
- 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 [236].
- 7) Probable Mechanism: additive CNS depression

3.5.1.CH] [Phenobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.CII [Phenytoin](#)

- 1) Interaction Effect: alterations in serum [phenytoin](#) concentrations
- 2) Summary: Use caution with the concomitant administration of [phenytoin](#) and [diazepam](#), as [phenytoin](#) levels may be decreased [224] [225] or increased [226]. Consider obtaining [phenytoin](#) serum concentrations if concomitant administration is necessary. [Phenytoin](#) dose adjustments may be required, especially with the addition or withdrawal of [diazepam](#) [224] [225].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Use caution with the concomitant administration of [phenytoin](#) and [diazepam](#), as [phenytoin](#) levels may be decreased [224] [225] or increased [226]. Consider obtaining [phenytoin](#) serum concentrations if concomitant administration is necessary. [Phenytoin](#) dose adjustments may be required, especially with the addition or withdrawal of [diazepam](#) [224] [225].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) [Phenytoin](#) toxicity occurred in a 44-year-old man who was given concomitant [diazepam](#) therapy. The patient complained of headache, [nystagmus](#), [diplopia](#), and ataxia and was admitted to the hospital. Aside from his long-standing seizure disorder, his past medical history was unremarkable. His antiepileptic regimen of [phenytoin](#), [phenobarbital](#), and [lamotrigine](#) had been unchanged for almost 5 months. Two weeks prior to admission his total [phenytoin](#) serum concentration was 8 mcg/mL. He was prescribed [amoxicillin](#) and [diazepam](#) 2 days prior to his hospital admission. His serum [phenytoin](#) concentration was 37 mcg/mL in the hospital. [Diazepam](#) and [phenytoin](#) were discontinued and the symptoms resolved [226].

3.5.1.CJ] Piperaquine

- 1) Interaction Effect: increased exposure of CYP2C19 substrates
- 2) Summary: Concurrent administration of piperaquine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperaquine, caution is advised with administration of a CYP2C19 substrate for up to 3 months after discontinuation of piperaquine therapy [218]. If concomitant administration is required, use caution and monitor the patient closely.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of piperaquine (a CYP2C19 inhibitor) and a CYP2C19 substrate may increase the exposure of the CYP2C19 substrate. Due to the long half-life of piperaquine, caution is advised with administration of a CYP2C19 substrate for up to 3 months after discontinuation of piperaquine therapy [218]. If concomitant administration is required, use caution and monitor the patient closely.
- 7) Probable Mechanism: inhibition of CYP2C19-mediated metabolism by piperaquine

3.5.1.CK] Primidone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.CL] Propofol

- 1) Interaction Effect: [diazepam](#) toxicity (CNS depression)
- 2) Summary: Concomitant use of [diazepam](#) 15 to 20 mg and [propofol](#) 100 to 150 mg has been reported to extend the sedative effects of [diazepam](#) [324].
- 3) Severity: minor

- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for excessive sedation and provide medical support if required.
- 7) Probable Mechanism: unknown

3.5.1.CM] Propoxyphene

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.CN] Quinupristin

- 1) Interaction Effect: an increased risk of [diazepam](#) toxicity (excessive sedation, confusion)
- 2) Summary: The concurrent administration of [quinupristin/dalfopristin](#) and [diazepam](#) may result in increased levels of [diazepam](#). [Quinupristin/dalfopristin](#) is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, and [diazepam](#) is a CYP3A4 substrate [266].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Coadministration of [quinupristin/dalfopristin](#) and [diazepam](#) should be undertaken with caution. Patients should be monitored for signs of excessive central nervous system depression. Doses of [diazepam](#) may need to be reduced.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [diazepam](#) metabolism

3.5.1.CO] Remifentanyl

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.CP] [Rifampin](#)

- 1) Interaction Effect: decreased [diazepam](#) effectiveness
- 2) Summary: In a controlled study, the addition of [rifampin](#) to [diazepam](#) treatment decreased the [diazepam](#) half-life from 58 hours to approximately 14 hours [316]. Patients also appeared to eliminate the desmethyldiazepam metabolite more rapidly ([halazepam](#), [clorazepate](#), and [prazepam](#) have a desmethyldiazepam metabolite) [317].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If concurrent therapy is required, a dosage adjustment for [diazepam](#) may be required in order to maintain or achieve a therapeutic effect. Dosage reduction may be required after discontinuing [rifampin](#).
- 7) Probable Mechanism: increased hepatic metabolism

3.5.1.CQ] [Rifapentine](#)

- 1) Interaction Effect: reduced [diazepam](#) plasma concentrations and effectiveness
- 2) Summary: Concurrent use of [rifapentine](#) and a benzodiazepine has resulted in reduced benzodiazepine serum concentrations and effectiveness. [Rifapentine](#) probably induces hepatic microsomal enzymes which metabolizes the benzodiazepine [361].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: If used concurrently, a dosage adjustment for the benzodiazepine may be required in order to maintain a therapeutic effect. Dosage reduction may be required after discontinuing [rifapentine](#).
- 7) Probable Mechanism: induction of benzodiazepine metabolism

3.5.1.CR] [Ritonavir](#)

- 1) Interaction Effect: an increased risk of extreme sedation and confusion
- 2) Summary: Coadministered [ritonavir](#) may increase serum concentrations of [diazepam](#), causing a potential risk of extreme sedation and [respiratory depression](#) [230]. A decrease in benzodiazepine dose may be needed [231].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for signs and symptoms of benzodiazepine toxicity (sedation, confusion, [respiratory depression](#)). Reduce doses of [diazepam](#) as required.

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

3.5.1.CS| Roxithromycin

1J) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)

2J) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [145] [146] [147] [148].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.

7J) Probable Mechanism: decreased hepatic metabolism; decreased clearance

8J) Literature Reports

aJ) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in one hour by intravenous [erythromycin](#) 400 mg. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 mg/mL [142].

bJ) In a study involving normal volunteers, [erythromycin](#) (333 mg three times daily for three days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from four to six hours, and decreased the volume of distribution [143].

cJ) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following five days of [erythromycin](#) therapy versus placebo [144].

3.5.1.CT| Saquinavir

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

2J) Summary: [Diazepam](#) is metabolized primarily by CYP3A4 [220] and [saquinavir](#) is a strong CYP3A4 inhibitor. Use caution with the concomitant use of [diazepam](#) and [saquinavir](#), and consider dose reductions of [diazepam](#) when necessary [221].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: theoretical

6J) Clinical Management: The concomitant use of [diazepam](#) and CYP3A inhibitors, such as [saquinavir](#), may lead to increased and prolonged sedation [220]. If coadministration is required, a dose reduction of [diazepam](#) may be warranted [221].

7J) Probable Mechanism: inhibition of CYP3A-mediated [diazepam](#) metabolism by [saquinavir](#)

3.5.1.CU| Secobarbital

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

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].
- 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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.CV] 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 [352] [353]. Theoretically, skullcap may have additive effects when administered with a benzodiazepine, yet if the binding is competitive in nature, skullcap may displace the benzodiazepine from the receptor and reduce its effectiveness. Caution is advised with concomitant use of skullcap and benzodiazepines until this potential interaction is better characterized.
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for increased central nervous system depression, and for altered effectiveness of benzodiazepine therapy.
- 7) Probable Mechanism: several constituents of skullcap have demonstrated binding affinity for the benzodiazepine site of the GABA-A receptor
- 8) Literature Reports

a) Constituents isolated from the organic solvent extract of skullcap root demonstrated binding affinity for the benzodiazepine (BZD) site of the GABA-A receptor. Wogonin and baicalein had the strongest affinity, scutellarein had moderate activity, and baicalin had weakest activity. All of these constituents contain the flavonoid phenylbenzopyrone nucleus, which binds to the benzodiazepine site. The concentrations at which 50 percent inhibition (IC₅₀) of (3H)flunitrazepam binding occurred were as follows, wogonin 3.62 micromolar (mcM); baicalein 10.11 mcM; scutellarein 20.96 mcM; and baicalin 137.07 mcM, whereas the IC₅₀ of [diazepam](#) was 0.029 mcM [350].

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](#) [351].

3.5.1.CW] [Sodium Oxybate](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [151]. 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.CX] [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 [248] [249] [250] [251]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [248]. 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 [248] [249] [250] [251]. 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_{max} and AUC were reduced by 8.7 nanograms (ng)/mL (95% confidence interval (CI), -17.1 to -0.2 ng/mL; p less than 0.05) and by 55 ng hr/mL (95% CI, -96 to -15 ng hr/mL; p less than 0.05), respectively, in the St. John's wort group compared with the placebo group. [Quazepam](#) T_{max} and t(1/2) and 2-oxoquazepam C_{max}, AUC, T_{max}, and t(1/2) were not significantly affected by St. John's wort. The 2-oxoquazepam to [quazepam](#) ratio in the C_{max} was higher in the St. John's wort group compared with the placebo group (0.47 vs 0.4 ng/mL; p less than 0.01). The urinary ratio of 6-beta-hydroxycortisol to cortisol was increased with St. John's wort compared with placebo (ratio, 2.1; 95% CI, 0.85 to 3.4; p less than 0.05); an increased urinary ratio of cortisol metabolite to cortisol is indicative of hepatic CYP3A4 activity. [Quazepam](#) efficacy was not significantly changed with the coadministration of St. John's wort as reflected in the visual analogue scale (VAS), which evaluates self-ratings of sedative-like effects, and the digit symbol substitution test (DSST) which measures psychomotor performance [248].

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) [249].

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 [252].

d)) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and C_{max} of oral [midazolam](#) were reduced by 50%, and oral clearance increased 2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [250].

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) [251].

3.5.1.CY] [Sufentanil](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [255]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [256]. 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](#) [223].
- 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 [254].

3.5.1.CZ] [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 [268].
- 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 [268].
- 7) Probable Mechanism: additive CNS depression

3.5.1.DA] [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 [336]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [336]. Because tan-shen acts as a partial and not a full agonist, the clinical significance of the interaction is unknown. Caution is advised until the magnitude of the interaction is better understood.

3) Severity: minor

4) Onset: delayed

5) Substantiation: theoretical

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

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

8) Literature Reports

a) Ten diterpene quinones present in the Chinese medicinal herb *Salvia miltiorrhiza* (tan-shen) have been shown to inhibit binding of (3H) flunitrazepam to central benzodiazepine receptors. These quinones, isolated from the ethereal extract of the roots of *Salvia miltiorrhiza*, exhibited IC₅₀s ranging from 0.3 to 36.2 μmol (the IC₅₀ is the drug concentration required to provide 50% inhibition of specific (3H) flunitrazepam binding). Miltirone had the highest potency (IC₅₀=0.3 μmol) [335]. 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](#) [335].

3.5.1.DB] 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 [219].

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 [219].

7) Probable Mechanism: additive effects

3.5.1.DC] 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 [294]. 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 [294]. 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 [294].

3.5.1.DD] [Theophylline](#)

1) Interaction Effect: decreased benzodiazepine effectiveness

2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [162] [163] [164] [165]. 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 [166].

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 [153].

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 [154]. Other studies and case reports have also shown that [theophylline](#) antagonizes the sedative effects of [diazepam](#) [155] [156].

c) Three case reports described patients who had the sedative effects of [lorazepam](#) reversed postoperatively by the administration of [aminophylline](#) 1 mg/kg intravenously [157]. This same [aminophylline](#) dose was used to reverse the sedative effects of [midazolam](#) in three other patients [158]. [Theophylline](#) also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [159].

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 [160].

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 [161].

3.5.1.DE] Thiopental

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [196] [197] [198] [199] [200].

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 [187] [188] [189] [190] [191].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [192]. 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 [193]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [194]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [195].

3.5.1.DF] Troleandomycin

1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)

2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [176] [177] [178] [179].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.

7) Probable Mechanism: decreased hepatic metabolism; decreased clearance

8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 ng/mL [173].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg TID for 3 days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [174].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following 5 days of [erythromycin](#) therapy versus placebo [175].

3.5.1.DG| [Valdecoxib](#)

1) Interaction Effect: increased plasma exposure to [diazepam](#) and increased sedative side effects of [diazepam](#)

2) Summary: Concomitant administration of [diazepam](#) with [valdecoxib](#) has resulted in an increased plasma exposure of [diazepam](#). Although this increase is not significant and does not require dose adjustments, sedative effects of [diazepam](#) may be increased. Patients should be cautioned about this effect and should be advised against performing any tasks that require complete mental alertness [201].

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for enhanced sedative side effects of [diazepam](#). Caution patients against performing hazardous activities that require complete mental alertness, such as operating machinery or driving a motor vehicle.

7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [diazepam](#) metabolism

8) Literature Reports

a) Concomitant administration of 10 milligrams (mg) [diazepam](#) twice daily with 40 mg [valdecoxib](#) twice daily for 12 days resulted in a 28% increase in plasma exposure of [diazepam](#). However, there were no significant changes in the plasma exposure of [valdecoxib](#) [201].

3.5.1.DH| 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 [285]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [293] [286]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [286]. 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 [285]. Monitoring for altered effectiveness of the benzodiazepine should be considered with concurrent use.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of valerian and benzodiazepines may result in additive CNS depressive effects or may decrease the effectiveness of benzodiazepines. It is recommended that patients be asked about herbal product use during intake of personal history [285] [286]. Monitor for altered effectiveness of the benzodiazepine during concurrent use.
- 7) Probable Mechanism: additive effects on the benzodiazepine receptor, possible displacement of the benzodiazepine from its receptor
- 8) Literature Reports

a) A case report describes a potentiated CNS depressive effect in a 40-year-old man following concomitant use of [lorazepam](#) with valerian and passionflower. The patient, who had been treating with [lorazepam](#) 2 mg/day for 2 months with no adverse effects, self-administered an infusion of valerian subterranean parts (estimated dose, 300 mg). 2 hours before going to bed for 2 consecutive days. On day 3, he instead ingested 3 oral tablets of dry extract from valerian rhizomes (300 mg/tablet) plus roots and aerial parts of passionflower (380 mg/tablet) at 1 hour intervals before bedtime. Nervousness and mild shaking dissipated after going to bed followed by extreme somnolence. After taking the same dose of the valerian root/passionflower product on day 4, he experienced more severe symptoms including substantial hand shaking, dizziness, and palpitations before bedtime followed by profound somnolence. Upon presentation after 32 hours of experiencing these CNS symptoms, he was observed to have nervousness while speaking and demonstrated anxious behavior without shaking. He had a history of general anxiety disorders and dream disorders. His family history was negative for essential tremor and there were no metabolic, renal, or hepatic disorders, high blood pressure, or drug allergies. Because a drug interaction was suspected, the patient was continued on [lorazepam](#) but withdrawn from valerian and passionflower and symptoms resolved. It is postulated that the valerian root and passionflower have additive or synergistic effects on the inhibitory activity of benzodiazepines binding to the [gamma-aminobutyric acid \(GABA\)](#) receptors [285].

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 [287] [288]. Valeriana officinalis extracts significantly displaced fluorodiazepam from benzodiazepine receptors, and a fraction containing sesquiterpene alcohols and ketones showed 80% inhibition

at concentrations of 1.5×10^{-3} moles/liter. A fraction containing valepotriates also produced significant displacement. Statistical values were not provided [289]. 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 [290]. 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 [291].

c) Hydroalcoholic and aqueous extracts of *Valeriana officinalis* roots showed affinity for the GABA-A receptors with lesser affinity for the peripheral benzodiazepine receptors in vitro. Inhibition of 3H-PK 11195 binding to benzodiazepine and GABA-A receptors was measured and expressed as IC₅₀ values. IC₅₀ values for the hydroalcoholic extract were 0.04 milligrams/milliliter (mg/ml) and 3.9×10^{-3} mg/ml for peripheral and central benzodiazepine receptors and GABA-A receptors, respectively. The lipophilic fraction of the hydroalcoholic extract showed affinity for the barbiturate receptor and to some extent for peripheral benzodiazepine receptors. The aqueous total extract A, the aqueous fraction B derived from the hydroalcoholic extracts, as well as the hydroalcoholic extracts demonstrated affinity for GABA-A receptors. This interaction at the receptor level could represent the molecular basis for the sedative effect noted with *Valeriana officinalis* [292].

3.5.1.DI] 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 [359].
- 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 [359].
- 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 diazepam
- 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 [374] [375] [376].
- 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 [373].

3.5.2.B) Ethanol

1) Interaction Effect: increased sedation

2) Summary: Coadministration of ethanol with [diazepam](#) results in higher plasma [diazepam](#) levels; the mechanism presumably is enhanced absorption [366]. Acute ethanol use can also decrease [diazepam](#) clearance by up to 50% [367] [368] [369]. This combination results in increased sedation and additive or synergistic effects in decreasing driving skills and general psychomotor performance.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Patients should be instructed to avoid ethanol ingestion while taking [diazepam](#).

7) Probable Mechanism: additive CNS depression

8) Literature Reports

a) Although the deleterious effect of [diazepam](#) plus ethanol on skilled performance is well documented [362] [363], ethanol-induced alterations in [diazepam](#) pharmacokinetic parameters have not been proven. In a placebo-controlled study conducted by [364], ethanol ingestion did not significantly increase [diazepam](#) absorption in 24 healthy males.

b) In another study, utilizing computer simulation, the effect of ethanol on benzodiazepine absorption and metabolism was investigated. Based on reported clinical data and the use of mathematical modeling, the investigators determined that ethanol caused a transient 75% decrease in benzodiazepine clearance which resulted in a 13.5% increase in the benzodiazepine area under the concentration-time curve (AUC), a 3.4% increase in maximum serum concentration, and a 5.7% increase in time to maximum serum concentration [365].

3.5.2.C) Grapefruit Juice

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

2) Summary: A study was conducted on eight healthy individuals to determine the effects of grapefruit juice on [diazepam](#) bioavailability. A single 5 mg dose of [diazepam](#) was given with 250 ml of either water or grapefruit juice, and blood levels were drawn at specific intervals thereafter. The peak concentrations of six of the eight subjects were increased, and the time to reach peak concentration was increased in all subjects [378].

3) Severity: moderate

4) Onset: rapid

- 5) Substantiation: probable
- 6) Clinical Management: Advise patient of possible increased [diazepam](#) effects if taken with grapefruit juice.
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4 enzymes responsible for [diazepam](#) metabolism
- 8) Literature Reports

a) In a study conducted by the University of Osmangazi in Turkey, eight healthy individuals were given a single 5 mg dose of [diazepam](#) with 250 ml of either water or grapefruit juice. Blood levels were drawn at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after administration. The study demonstrated an increase in the areas under the concentration-time curve (AUC) of 3.2 times after grapefruit juice and [diazepam](#) administration, versus water and [diazepam](#). In addition, the peak concentrations (C_{max}) of six of the eight subjects were increased 1.5 times, and the time to reach peak concentration (t_{max}) was increased from 1.5 hours to 2.06 hours. This study demonstrates that grapefruit juice can increase the plasma concentrations and therefore, the effects of oral [diazepam](#) [377].

3.5.2.D) High Fat Food

- 1) Interaction Effect: increased [diazepam](#) concentrations
- 2) Summary: Serum [diazepam](#) levels have been shown to be significantly increased when the administration of intravenous [diazepam](#) is followed by a high-fat meal. This effect may be attributed to an enterohepatic cycle of [diazepam](#) [371]. However, food intake has been shown to not alter the plasma binding of [diazepam](#) [372].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: If possible, the administration of [diazepam](#) should not be followed by a high-fat meal. Monitor the patient for excessive sedation and lethargy.
- 7) Probable Mechanism: increased enterohepatic circulation of [diazepam](#)
- 8) Literature Reports

a) A study investigated the effects of three diets (olestra, [triglyceride](#) oil, and water) on the bioavailability of oral [propranolol](#) (20 mg), [diazepam](#) (5 mg), and [ethinyl estradiol/norethindrone](#) ([Brevicon®](#)). The absorption of the three agents was essentially unaffected when given with olestra, [triglyceride](#) oil, or water. However, the time to peak concentration for [diazepam](#) was significantly longer with [triglyceride](#) oil as compared to olestra or water [370].

b) In one study, seven healthy volunteers were administered [diazepam](#) 0.3 mg/kg intravenously three times at intervals of 14 days. Five hours after each injection, the subjects received either 330 mL of mineral water, mineral water in combination with two rusks, or 330 mL of fatty milk with an egg hamburger. One hour after the administration of rusks or an egg hamburger, serum [diazepam](#) levels were significantly elevated compared to the levels measured after mineral water. This finding supports an enterohepatic cycle of [diazepam](#) [371].

c) Others investigated the possibility that food intake might influence the plasma levels of [diazepam](#) via changes in plasma binding. Plasma samples from five volunteers were collected one hour before and one and two hours after lunch. There was no significant change in [diazepam](#) plasma binding before and after lunch. This study suggests that normal food consumption does not alter the plasma binding of [diazepam](#) [372].

3.5.5] Intravenous Admixtures

3.5.5.1] Drugs

3.5.5.1.A] Acetaminophen

1) Incompatible

a) Acetaminophen with diazepam in a 50:50 admixed ratio was physically incompatible at room temperature for up to 4 hours 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 [866].

3.5.5.1.B] Atracurium

1) Incompatible

a) Atracurium (500 mcg/mL with diazepam 5 mg/mL, immediate formation of a cloudy solution reported) [864]

b) Diazepam (5 mg/mL with atracurium 500 mcg/mL, immediate formation of a cloudy solution reported) [865]

3.5.5.1.C] Benzquinamide

1) Incompatible

a) Benzquinamide 25 mg/1 mL with diazepam 10 mg/2 mL, immediate physical incompatibility observed [915]

b) Benzquinamide 50 mg/2 mL with diazepam 10 mg/2 mL, immediate physical incompatibility observed [915]

c) Benzquinamide 50 mg/1 mL with diazepam 10 mg/2 mL, immediate physical incompatibility observed [915]

3.5.5.1.D] Bivalirudin

1) Incompatible

a) The mixture of bivalirudin with diazepam, when administered in the same intravenous line, has resulted in microparticulate formation, haze formation, or gross precipitation; conditions were not specified [872].

3.5.5.1.E] Bleomycin Sulfate

1) Incompatible

a) Bleomycin sulfate 20 or 30 U/L with diazepam 50 or 100 mg/L, physically incompatible although bleomycin activity retained for 1 week at 4 degrees C in Sodium chloride 0.9% [895]

3.5.5.1.F] Buprenorphine

1) Incompatible

- a) **Buprenorphine** with **diazepam** in a 1:1 volume ratio, incompatible at room temperature [906]

3.5.5.1.G) Butorphanol**1) Incompatible**

- a) **Butorphanol** 1 or 2 mg/mL with **diazepam** 5 mg/mL, visually incompatible [902]

3.5.5.1.H) Ceftaroline Fosamil**1) Incompatible**

- a) Ceftaroline fosamil 2.22 mg/mL (diluted with either 0.9% **sodium chloride**, 5% **dextrose**, or lactated Ringer injection) and **diazepam** 5 mg/mL (undiluted) were incompatible (dense turbid precipitate) within 4 hours at room temperature (23 degrees C) under fluorescent light during simulated Y-site administration [913].

3.5.5.1.I) Cimetidine**1) Compatible**

- a) **Cimetidine** 300 mg/2 mL with **diazepam** 10 mg/2 mL visually compatible in direct admixture in syringe for 4 hours at 25 degrees C [861]

3.5.5.1.J) Diatrizoate Meglumine**1) Incompatible**

- a) **DIATRIZOATE MEGLUMINE** 5 mL of a solution containing **iodine** 282 mg/mL with **diazepam** 5 mg/mL, resulted a white suspension that persisted longer than 1 minute [898]

3.5.5.1.K) Diatrizoate Sodium**1) Compatible**

- a) **DIATRIZOATE SODIUM** 5 mL of a solution containing **iodine** 300 mg/mL with **diazepam** 5 mg/mL, no change after mixing [896]

3.5.5.1.L) Dobutamine**1) Incompatible**

- a) **Dobutamine** (1 g/L with **diazepam** 2.5 g/L, rapid formation of a cloudy solution reported with yellow precipitate formation reported at 24 hours at 21 degrees C under fluorescent light in **Dextrose** 5% in water or **Sodium chloride** 0.9%) [862]
- b) **Diazepam** (2.5 g/L with **dobutamine** 1 g/L immediate turbidity with formation of yellow precipitate within 24 hours at 21 degrees C in **Dextrose** 5% in water or **Sodium chloride** 0.9%) (Hasegawa & Eder, 1984)

3.5.5.1.M) Doripenem

1) Incompatible

a) **Diazepam** 5 mg/mL (tested undiluted) with doripenem 5 mg/mL (diluted in either 5% **dextrose** injection or in 0.9% **sodium chloride** injection) is physically incompatible, as a simulated Y-site administration at room temperature (approximately 23 degrees C) and under fluorescent lights resulted in the immediate formation of a gross white turbid precipitation which persisted for 4 hours [914].

3.5.5.1.N] Doxapram**1) Incompatible**

a) **Diazepam** (10 mg/2 mL with **doxapram** 400 mg/20 mL, immediate turbidity and precipitate formation reported in syringe) [869]

3.5.5.1.O] Doxorubicin**1) Incompatible**

a) **Diazepam** (with **doxorubicin**, immediate precipitate formation reported; drug concentrations and conditions not specified) [874]

b) **Doxorubicin** (with **diazepam**, concentrations not specified, immediate precipitate formation reported) [875]

3.5.5.1.P] Esmolol**1) Incompatible**

a) **Diazepam** (incompatible with **esmolol**; conditions not specified) [870]

b) **Esmolol** (incompatible with **diazepam**; conditions not specified) [871]

3.5.5.1.Q] Fenoldopam Mesylate**1) Incompatible**

a) **Diazepam** 5 mg/mL (undiluted) with **fenoldopam** mesylate 80 mcg/mL in **Sodium chloride** 0.9% injection, trace haze and micro-particulates formed immediately when admixed; yellow discoloration and visible turbidity developed within 4 hours during simulated Y-site administration [899].

3.5.5.1.R] Fluconazole**1) Incompatible**

a) **Diazepam** 5 milligrams/milliliter (mg/mL) with **fluconazole** 2 mg/mL, visually incompatible, immediate precipitation reported [904]

3.5.5.1.S] Fluorouracil**1) Incompatible**

a) **Diazepam** (with **fluorouracil**, immediate precipitate formation reported; drug concentrations and test conditions not specified) [873]

b)) Fluorouracil (with diazepam, concentrations not specified, precipitate formation reported) (Tech Info Cetus, 1988)

3.5.5.1.T] Foscarnet

1)) Incompatible

a)) Diazepam 5 mg/mL with foscarnet 24 mg/mL, gas production reported [901]

3.5.5.1.U] Glycopyrrolate

1)) Incompatible

a)) Diazepam with glycopyrrolate physically incompatible in syringe at 25 degrees C; specific drug concentrations listed below [900]:

diazepam 5 mg/1 mL with glycopyrrolate 200 mcg/1 mL

diazepam 5 mg/1 mL with glycopyrrolate 400 mcg/2 mL

diazepam 10 mg/2 mL with glycopyrrolate 200 mcg/1 mL

3.5.5.1.V] Haloperidol

1)) Incompatible

a)) Diazepam in a 1:1 or 2:1 mixture with haloperidol, precipitate formation reported within 2 hours at room temperature; drug concentrations not specified [863]

3.5.5.1.W] Heparin

1)) Incompatible

a)) Diazepam 5 mg/mL with hydrocortisone sodium succinate 100 mg/L and heparin 1000 U/L, immediate haziness and globule formation reported in the following solutions [884]:

Dextrose 5% in water

Lactated Ringer's injection

Sodium chloride 0.9%

b)) Diazepam 10 mg/2 mL - administered over 3 minutes into a heparin infusion run at 1 mL/min - with heparin 50 U/mL/min, turbidity reported [903]

c)) Diazepam 10 mg/2 mL with heparin 2500 U/1 mL, turbidity or precipitate formation reported within 5 minutes in syringe [903]

3.5.5.1.X] Hydrocortisone Sodium Succinate

1)) Incompatible

a) **Diazepam** 5 mg/mL with **hydrocortisone** sodium succinate 100 mg/L and **heparin** 1000 U/L, immediate haziness and globule formation reported in the following solutions [884]:

Dextrose 5% in water

Lactated Ringer's injection

Sodium chloride 0.9%

3.5.5.1.Y] **Hydroxocobalamin**

1) Incompatible

a) The mixture of **diazepam** with **hydroxocobalamin** (2.5 g/100 mL), when administered in the same intravenous line, has resulted in particle formation [912].

3.5.5.1.Z] **Iodine**

1) Conflicting Data

a) Incompatible

1) **DIATRIZOATE MEGLUMINE** 5 mL of a solution containing **iodine** 282 mg/mL with **diazepam** 5 mg/mL, resulted a white suspension that persisted longer than 1 minute [898]

b) Compatible

1) **Diazepam** 5 mg/mL with **ioxaglate** 5 mL of a solution containing **iodine** 320 mg/mL, no change after mixing [860]

2) **Diazepam** 5 mg/mL with **iohexol** 5 mL of solution containing **iodine** 300 mg/mL, no change after mixing [878]

3) **DIATRIZOATE SODIUM** 5 mL of a solution containing **iodine** 300 mg/mL with **diazepam** 5 mg/mL, no change after mixing [896]

4) **Diazepam** 5 mg/mL with **iothalamate** 5 mL of a solution containing **iodine** 282 mg/mL, no change after mixing [897]

5) **Diazepam** 5 mg/mL with **iopamidol** 5 mL of a solution containing **iodine** 300 mg/mL, no change after mixing [905]

3.5.5.1.AA] **Iohexol**

1) Compatible

a) **Diazepam** 5 mg/mL with **iohexol** 5 mL of solution containing **iodine** 300 mg/mL, no change after mixing [878]

3.5.5.1.AB] Iomeprol**1) Compatible**

a) Iomeprol 5 mL (400 mg iodine per mL) was mixed with diazepam 5 mL and 10 mL (5 mg/mL) and clarity was checked immediately and after 10, 60, and 120 minutes. No formation of precipitate was noted at any observation time [867].

3.5.5.1.AC] Iopamidol**1) Compatible**

a) Diazepam 5 mg/mL with iopamidol 5 mL of a solution containing iodine 300 mg/mL, no change after mixing [905]

3.5.5.1.AD] Iothalamate**1) Compatible**

a) Diazepam 5 mg/mL with iothalamate 5 mL of a solution containing iodine 282 mg/mL, no change after mixing [897]

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

a) Diazepam 5 mg/mL mixed with ioversol 68% in a 1:10 or 1:1 ratio exhibited no significant physical changes in 1 hour at room temperature [885]

3.5.5.1.AF] Ioxaglate**1) Compatible**

a) Diazepam 5 mg/mL with ioxaglate 5 mL of a solution containing iodine 320 mg/mL, no change after mixing [860]

3.5.5.1.AG] Ketorolac Tromethamine**1) Incompatible**

a) Diazepam 5 mg/mL with ketorolac tromethamine 30 mg/mL, no precipitation observed, however, spectrophotometric changes reported; therefore mixing of these 2 drugs were not recommended [887]

3.5.5.1.AH] Linezolid**1) Incompatible**

a) Diazepam 5 mg/mL with linezolid 2 mg/mL (both tested undiluted) is physically incompatible, as a simulated Y-site administration at room temperature (approximately 23 degrees C) and under fluorescent light resulted in the immediate formation of a turbid precipitate which persisted for 4 hours [888].

3.5.5.1.AI] Meropenem

1) Incompatible

- a) **Diazepam** 10 mg/mL combined with **meropenem** at a concentration of either 1 mg/mL or 50 mg/mL formed an immediate precipitate [877].

3.5.5.1.AJ] Nafcillin**1) Compatible**

- a) **Nafcillin** (33 mg/mL with **diazepam** 5 mg/mL, no p precipitate formation reported in **Sodium chloride** 0.9%; conditions not specified) [907]
- b) **Diazepam** (5 mg/mL with **nafcillin** 33 mg/mL no precipitate formation reported in **Sodium chloride** 0.9%; conditions not specified) [908]

3.5.5.1.AK] Nalbuphine**1) Incompatible**

- a) **Diazepam** 5 mg/1 mL with **nalbuphine** 2.5 mg/0.25 mL, 5 mg/0.5 mL, or 10 mg/1 mL, immediate formation of a white precipitate that, in lower **nalbuphine** concentrations, clears upon vigorous shaking and remains clear for 36 hours at 27 degrees C; in highest **nalbuphine** concentration, however, precipitate persists for 36 hour study period [911]

3.5.5.1.AL] Netilmicin**1) Compatible**

- a) **Netilmicin** (3 g/L with **diazepam** 40 mg/L visually compatible and **netilmicin** chemically stable for 7 days at 4 or 25 degrees C in **Dextrose** 5% in **sodium chloride** 0.9%; **diazepam** stability not tested) [890]
- b) **Diazepam** (40 mg/L with **netilmicin** 3 g/L visually compatible and **netilmicin** bioactivity retained for 7 days at 4 or 25 degrees C in **Dextrose** 5% in **sodium chloride** 0.9%; **diazepam** concentration not tested) [891]

3.5.5.1.AM] Pancuronium**1) Incompatible**

- a) **Diazepam** 5 mg/mL with **pancuronium** 0.05 mg/mL, immediate formation of a cloudy solution reported [889]

3.5.5.1.AN] Potassium Chloride**1) Incompatible**

- a) **Diazepam** (5 mg/mL with potassium **chloride** 40 mEq/L, immediate haziness and globule formation reported in the following solutions) [893]:

Dextrose 5% in water

Lactated Ringer's injection

Sodium chloride 0.9%

b) Potassium [chloride](#) (40 mEq/L with [diazepam](#) 5 mg/mL, immediate haziness and globule formation reported in the following solutions) [894]:

Dextrose 5% in water

Lactated Ringer's injection

Sodium chloride 0.9%

3.5.5.1.AO] [Propofol](#)

1) Incompatible

a) [Propofol](#) 1% injectable emulsion and [diazepam](#) 5 milligrams/milliliter in a 1:1 volume mixture (simulated Y-site administration) are visually incompatible 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) [886]. The emulsion immediately broke and oiled out.

3.5.5.1.AP] [Quinidine Gluconate](#)

1) Compatible

a) [Diazepam](#) 0.2 mg/mL with [quinidine](#) gluconate 6 mg/mL, both in [Dextrose](#) 5% in water or both in [Sodium chloride](#) 0.9%, no observed evidence of incompatibility over 3 hours in glass containers at ambient laboratory temperature under constant fluorescent light [883]

3.5.5.1.AQ] [Ranitidine](#)

1) Conflicting Data

a) Incompatible

1) [Diazepam](#) 10 mg/1 mL with [ranitidine](#) 50 mg/2 mL, physically compatible in syringe for 1 hour at 25 degrees C under fluorescent light; however a transient haze was reported which disappeared following vortex mixing [881]

2) [Diazepam](#) 10 mg, volume not stated with [ranitidine](#) 50 mg/5 mL, physically compatible in syringe for 4 hours at ambient temperature under fluorescent light [882]

b) Compatible

1) [Diazepam](#) 10 mg/1 mL with [ranitidine](#) 50 mg/2 mL, physically compatible in syringe for 1 hour at 25 degrees C under fluorescent light; however a transient haze was reported which disappeared following vortex mixing [879]

2) [Diazepam](#) 10 mg, volume not stated with [ranitidine](#) 50 mg/5 mL, physically compatible in syringe for 4 hours at ambient temperature under fluorescent light [880]

3.5.5.1.AR] Rapacuronium**1) Incompatible**

- a) Rapacuronium is physically incompatible with [diazepam](#); drug concentration and conditions not specified [892].

3.5.5.1.AS] Tigecycline**1) Incompatible**

- a) [Diazepam](#) and [tigecycline](#) (diluted with either 0.9% [sodium chloride](#) or 5% [dextrose](#)) are not compatible for simultaneous administration via Y-site infusion and must be administered separately when concomitant therapy is indicated [909].

3.5.5.1.AT] Tirofiban**1) Incompatible**

- a) [Diazepam](#) and [tirofiban](#) should not be administered in the same intravenous line [910].

3.5.5.1.AU] Vecuronium**1) Incompatible**

- a) [Diazepam](#) 5 mg/mL with vecuronium 0.1 mg/mL, immediate formation of a cloudy solution reported [876]

3.5.5.1.AV] Verapamil**1) Compatible**

- a) [Diazepam](#) 20 mg/L with [verapamil](#) 80 mg/L, visually compatible for 24 hours in [Dextrose](#) 5% in water or [Sodium chloride](#) 0.9%; no temperature specified [868]

3.5.5.1.AW] Vitamin B Complex/Ascorbic Acid**1) Incompatible**

- a) Vitamin B complex with C (2 mL/L with [diazepam](#) 5 mg/mL, immediate haziness and globule formation reported in the following solutions) [894]:

Dextrose 5% in water

Lactated Ringer's injection

Sodium chloride 0.9%

3.5.5.2] Solutions**3.5.5.2.A] [Dextrose](#) 5% in water****1) Conflicting Data**

a) Incompatible

- 1) **Dextrose** 5% in water with **diazepam** 40 mg/L, no precipitate formation, but 12% to 14% **diazepam** loss in 1 hour at room temperature or 5 degrees C in polyvinylchloride containers [921]; however, other studies found certain **diazepam** admixtures to be compatible.
- 2) **Dextrose** 5% in water with **diazepam** 50, 100, or 200 mg/L in polyvinylchloride containers, significant **diazepam** loss due to **adsorption** reported within 30 minutes to 2 hours at room temperature [922] [923] [924]
- 3) **Dextrose** 5% in water with **diazepam** 250 mg/L, visually compatible in glass containers for 24 hours, but 6% **diazepam** potency loss in 4 hours; **Dextrose** 5% in water with **diazepam** 333 mg/L or greater in glass containers, immediate precipitate formation reported [925]
- 4) **Dextrose** 5% in water with **diazepam** 370 mg/L, precipitate formed when Roche's **Valium**(R) or Dumex' Stesolid(R) was used, although Apotekernes Laboratorium's **Diazepam** AL(R) produced only cloudiness; using **thin-layer chromatography**, the author's found the **diazepam** concentration was retained in all 3 admixtures and attributed the precipitation to benzoates; conditions not specified [926]
- 5) **Dextrose** 5% in water 50 mL with **diazepam** powder 15 mg/mL in absolute alcohol or **diazepam** injection 5 mg/mL, **diazepam** solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding **diazepam** injection solutions [927]
- 6) [928] recommended that in preparing **diazepam** intravenous solutions, the diluent be added to the **diazepam** injection (and not **diazepam** to the diluent).

b) Compatible

- 1) **Dextrose** 5% in water with **diazepam** 40 mg/L, visually compatible and 10% **diazepam** loss in 24 hours at room temperature in a polyethylene container [916]; however, greater **diazepam** loss was reported in different concentrations of these additives.
- 2) **Dextrose** 5% in water with **diazepam** 50 or 67 mg/L, visually compatible and 0% to 1% **diazepam** loss in 24 hours in glass containers; **Dextrose** 5% in water with **diazepam** 100 or 125 mg/L, visually compatible and 8% to 10% **diazepam** loss in 24 hours in glass containers; temperature not specified [917]
- 3) **Dextrose** 5% in water with **diazepam** 200 mg/L, visually compatible and no significant change in **diazepam** concentration in 24 hours at 25 degrees C in glass or polyethylene containers [918]
- 4) **Dextrose** 5% in water 50 mL with **diazepam** powder 15 mg/mL in absolute alcohol or **diazepam** injection 5 mg/mL, **diazepam** solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding **diazepam** aqueous injection solutions [919]

5)) [920] recommended that in preparing diazepam intravenous solutions, the diluent be added to the diazepam injection (and not diazepam to the diluent).

3.5.5.2.B) LACTATED RINGER'S INJECTION

1)) Conflicting Data

a)) Incompatible

1)) Lactated Ringer's injection (with diazepam 50 mg/L, 40% diazepam potency loss in 30 minutes and 78% loss in 24 hours at room temperature in polyvinylchloride containers; with diazepam 100 mg/L, 35% diazepam potency loss in 30 minutes and 89% loss in 24 hours at room temperature in polyvinylchloride containers) [932]; (with diazepam 250 mg/L, precipitate formation reported in 8 to 12 hours and 5% diazepam potency loss reported in 4 hours in glass containers; with diazepam 333 mg/L or greater in glass containers, immediate precipitate formation reported) [444]

b)) Compatible

1)) Diazepam 50 or 67 mg/L in lactated Ringer's injection, visually compatible and 6% diazepam loss in 24 hours in glass container; diazepam 100 or 125 mg/L in lactated Ringer's injection, visually compatible and 8% to 10% diazepam loss in 24 hours in glass container [929]

2)) Diazepam 200 mg/L in lactated Ringer's injection, transient cloudiness reported followed by a clear solution [930]

3)) Diazepam powder 15 mg/mL in absolute alcohol or diazepam injection 5 mg/mL with lactated Ringer's injection 50 mL, diazepam solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding diazepam aqueous injection solutions [931]

3.5.5.2.C) RINGER'S INJECTION

1)) Conflicting Data

a)) Incompatible

1)) Ringer's injection (with diazepam 50 mg/L, 29% diazepam potency loss in 30 minutes and 78% loss in 24 hours at room temperature in polyvinylchloride containers; with diazepam 100 mg/L, 38% diazepam potency loss in 30 minutes and 89% loss in 24 hours at room temperature in polyvinylchloride containers) [932]; (with diazepam 250 mg/L, precipitate formation reported in 6 to 8 hours and 8% diazepam potency loss reported in 4 hours in glass containers; with diazepam 333 mg/L or greater in glass containers, immediate precipitate formation reported) [444]

b)) Compatible

1)) Ringer's injection (with diazepam 50 or 67 mg/L visually compatible and 0% to 3% diazepam loss in 24 hours in glass containers; with diazepam 100 or 125 mg/L

visually compatible and 7% to 12% diazepam loss in 24 hours in glass containers; temperature not specified) [444]

3.5.5.2.D) Sodium chloride 0.9%

1) Conflicting Data

a) Incompatible

- 1) Diazepam 10 to 80 mg/L in Sodium chloride 0.9%, no precipitate formation, but 12% to 20% diazepam loss in 1 hour at room temperature or 5 degrees C in polyvinylchloride containers [941]
- 2) Diazepam 50, 100, or 200 mg/L in Sodium chloride 0.9% in polyvinylchloride containers, significant diazepam loss due to adsorption reported within 30 minutes to 2 hours at room temperature [942] [943] [944]
- 3) Diazepam 250 mg/L in Sodium chloride 0.9%, visually compatible in glass containers for 24 hours, but 6% diazepam potency loss reported in 4 hours; diazepam 333 mg/L in Sodium chloride 0.9% or greater in glass containers, immediate precipitate formation reported [945] [946]
- 4) Diazepam powder 15 mg/mL in absolute alcohol or diazepam injection 5 mg/mL with Sodium chloride 0.9% 50 mL, diazepam solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding diazepam aqueous injection solutions [947]
- 5) [948] recommended that in preparing diazepam intravenous solutions, the diluent be added to the diazepam injection (and not diazepam to the diluent).

b) Compatible

- 1) Diazepam 10 mg/L in Sodium chloride 0.9%, visually compatible and 1% diazepam loss in 24 hours at room temperature in polyethylene containers [933]; however, this admixture has been found incompatible under certain conditions.
- 2) Diazepam 40 mg/L in Sodium chloride 0.9%, visually compatible and 1% to 4% diazepam loss in 24 hours at 5 degrees C or room temperature in glass or polyethylene containers [933]
- 3) Diazepam 80 mg/L in Sodium chloride 0.9%, visually compatible and 5% diazepam loss in 6 hours at room temperature; diazepam concentration at 24 hours not stated [933]
- 4) Diazepam 50 mg/L in Sodium chloride 0.9%, no diazepam reduction in glass containers and 5% diazepam loss in polyethylene containers in 7 days at 25 degrees C [934]
- 5) Diazepam 50, 67, 100, or 125 mg/L in Sodium chloride 0.9%, visually compatible and 1% to 7% diazepam loss in 24 hours in glass containers; temperature not specified [935]

6)) Diazepam 100 or 200 mg/L in Sodium chloride 0.9%, solution remained clear for 10 days in glass containers; temperature not specified [936]

7)) Diazepam 200 mg/L in Sodium chloride 0.9%, visually compatible with no significant reduction of diazepam concentration in 24 hours at 25 degrees C in glass or polyethylene containers [937]

8)) Diazepam 10 mg in Sodium chloride 0.9% 250 mL or diazepam 5 mg in Sodium chloride 0.9% 50 mL, no visible incompatibility with the latter admixture exhibiting no precipitation for one hour; conditions not specified; the solubility of diazepam was reported to be 10 mg/4 mL water [938]

9)) Diazepam powder 15 mg/mL in absolute alcohol or diazepam injection 5 mg/mL with Sodium chloride 0.9% 50 mL, diazepam solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding diazepam aqueous injection solutions [939]

10)) [940] recommended that in preparing diazepam intravenous solutions, the diluent be added to the diazepam injection (and not diazepam to the diluent).

3.5.5.2.E] STERILE WATER FOR INJECTION

1)) Conflicting Data

a)) Incompatible

1)) Diazepam powder 15 mg/mL in absolute alcohol or diazepam injection 5 mg/mL with Sterile water for injection 50 mL, diazepam solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding diazepam aqueous injection solutions [950]

b)) Compatible

1)) Diazepam powder 15 mg/mL in absolute alcohol or diazepam injection 5 mg/mL with Sterile water for injection 50 mL, diazepam solubility was found to be 0.04 to 0.05 mg/mL and the data suggested a 1:100 dilution when compounding diazepam aqueous injection solutions [949]

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

1J) Improvement in the signs and symptoms of the condition being treated is indicative of therapeutic effectiveness.

BJ) Toxic

1J) Excessive CNS sedation/depression; blood pressure and respiratory rate with IV administration should be monitored for toxic effect.

2J) Periodic blood counts and liver functions tests.

4.2J Patient Instructions

AJ) Diazepam (By mouth)

Diazepam

Treats anxiety, muscle spasms, and seizures.

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 diazepam](#), if you are pregnant, or if you have [narrow-angle glaucoma](#) or untreated [open-angle glaucoma](#), [myasthenia gravis](#), [sleep apnea](#) or severe breathing problems, or severe liver disease.

How to Use This Medicine:

Tablet, Liquid

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

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

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

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

Do not freeze the oral liquid.

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 [diazepam](#) works. Tell your doctor if you are also using any of the following:

[Theophylline](#)

A phenothiazine, such as [chlorpromazine](#), [perphenazine](#), [promethazine](#), [prochlorperazine](#), [thioridazine](#)

An MAO inhibitor

Medicine to treat depression or mental illness

Medicine for seizures

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:

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.

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

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.

Too much of this medicine can cause death. Symptoms of an overdose include extreme dizziness or weakness, trouble breathing, slow heartbeat, seizure, and cold, clammy skin.

This medicine may make you dizzy or drowsy. Do not drive or doing anything else that could be dangerous if you are not alert.

Your doctor will do lab tests at regular visits to check on the effects of this medicine. 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:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Lightheadedness, dizziness, fainting

Seizures

Confusion, severe drowsiness, trouble breathing, muscle weakness

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

Mild nausea

Tiredness

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

B) Diazepam (Injection)

Diazepam

Treats anxiety, muscle spasms, and certain types of seizure. This medicine is a benzodiazepine.

When This Medicine Should Not Be Used:

You should not receive this medicine if you have ever had an **allergic reaction** to **diazepam** or to similar medicines (such as **Restoril®**, **Xanax®**). You should not receive this medicine if you are pregnant, or if you have untreated **glaucoma**.

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 as a shot into a muscle or into a vein.

A nurse or other trained health professional 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 also using **cimetidine (Tagamet®)**, **theophylline**, an MAO inhibitor (**Eldepryl®**, **Marplan®**, **Nardil®**, **Parnate®**), medicine for depression (such as **Luvor®**, **Paxil®**, **Prozac®**, **Serzone®**, **Zoloft®**), phenothiazines (such as **Compazine®**, **Phenergan®**, **Serentil®**, **Thorazine®**), medicine for seizures (such as **Depakote®**, **Dilantin®**, **Keppra™**, **Luminal®**, **Tegretol®**), or any medicine to treat mental illness.

Do not drink alcohol while you are using this medicine.

Make sure your doctor knows if you are using any medicines that make you sleepy (such as sleeping pills, cold and allergy medicine, narcotic pain relievers, or sedatives).

Warnings While Using This Medicine:

Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.

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

This medicine may be habit-forming. If you feel that the medicine is not working as well, do not take more than your prescribed dose. Call your doctor for instructions.

Taking too much of this medicine can cause death. Symptoms of an overdose include: Extreme dizziness or weakness, shortness of breath, slow heartbeat, seizures, and cold, clammy skin.

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:

- Lightheadedness or fainting

- Seizures

- Severe confusion, drowsiness, or muscle weakness

- Severe nausea or vomiting, stomach pain, increased sweating

- Tremors or muscle cramps

- Yellow skin or eyes

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

- Blurred vision

- Hangover feeling

- Mild nausea

- Pain, swelling, itching, or irritation where the shot is given

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

C) [Diazepam](#) (Rectal)

[Diazepam](#)

Treats a type of seizure called "cluster seizures" in people who have [epilepsy](#). This medicine is used together with other medicines for seizures. This medicine is a benzodiazepine.

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [diazepam](#), or if you are pregnant or you have [narrow-angle glaucoma](#).

How to Use This Medicine:

Gel/Jelly

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

Never take rectal medicine by mouth.

This medicine is not to be used every day. After you use the medicine for a seizure, it is best to wait at least 5 days before using it again. Do not use this medicine for more than 5 seizures per month, unless your doctor tells you to.

This medicine will need to be given to you while you are having a seizure. A family member or other caregiver will give the medicine to you, since you will be unable to give it to yourself. It is very important for your caregiver to understand how and when to use this medicine. Read and follow the patient/caregiver instructions carefully. Ask your doctor or pharmacist if you or your caregiver have any questions.

This medicine comes in a prefilled plastic applicator. Remove the cap from the prefilled applicator before inserting it. To make the applicator easier to insert, use the lubricating gel that comes with the medicine.

Before using the [Diatat® Acudial™](#) syringe, make sure you can see the prescribed dose in the dose display window and that it is correct. Also, look for the green "ready" band on the syringe before inserting it. If the dose is not correct, or if the green band is not on the syringe, call your doctor or pharmacist right away.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Flush all leftover medicine down the toilet after you have finished your treatment. Also flush old medicine after the expiration date has passed. This medicine is one of only a few medicines that should be disposed of this way. Ask your pharmacist about the best way to dispose of the used medicine applicator and container. Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:

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

Make sure your doctor knows if you are also using other medicine for seizures (such as [carbamazepine](#), [phenobarbital](#), [phenytoin](#), [valproate](#), [Depakene®](#), [Dilantin®](#), [Tegretol®](#)), phenothiazine medicines (such as [prochlorperazine](#), [Compazine®](#), [Mellaril®](#), [Phenergan®](#), [Thorazine®](#), [Trilafon®](#)), an MAO inhibitor (such as [tranlycypromine](#), [Eldepryl®](#), [Marplan®](#), [Nardil®](#), [Parnate®](#)), or medicine for depression (such as [amitriptyline](#), [Effexor®](#), [Paxil®](#), [Zoloft®](#)).

Tell your doctor if you are also using [cimetidine](#) ([Tagamet®](#)), [quinidine](#), [ketoconazole](#) ([Nizoral®](#)), [troleandomycin](#) ([Tao®](#)), [clotrimazole](#) ([Femcare®](#)), [rifampin](#) ([Rimactane®](#)), [dexamethasone](#) ([Decadron®](#)), [omeprazole](#) ([Prilosec®](#)), [propranolol](#) ([Inderal®](#)), [imipramine](#) ([Tofranil®](#)), [cyclosporine](#) ([Gengraf®](#), [Neoral®](#), [Sandimmune®](#)), [paclitaxel](#) ([Taxol®](#)), [terfenadine](#) ([Seldane D®](#)), [theophylline](#) ([Theo-Dur®](#)), or a blood thinner such as [warfarin](#) ([Coumadin®](#)).

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:

Make sure your doctor knows if you are pregnant or may become pregnant. Using this medicine during pregnancy could affect your unborn baby. However, it may be important for you to use this medicine to control your seizures during pregnancy. Carefully follow your doctor's instructions. Tell your doctor right away if you become pregnant.

Make sure your doctor knows if you are breastfeeding, or if you have [kidney disease](#), liver disease, breathing problems, [glaucoma](#), or a history of drug or alcohol problems.

This medicine should be used only for the specific kind of cluster seizure for which it was prescribed. Do not use this medicine for any other type of seizure.

Make sure any doctor or dentist who treats you knows that you are using this medicine.

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

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

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

Increased energy, anxiety, nervousness, anger, or muscle spasms.

Seeing, hearing, or feeling things that are not there.

Severe confusion, drowsiness, or muscle weakness.

Severe nausea or vomiting, stomach pain, or increased sweating.

Tremors or muscle cramps.

Trouble breathing.

Trouble sleeping.

Unusual or increased seizure symptoms or a seizure that does not stop.

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

Clumsiness or dizziness.

Diarrhea.

Headache.

Skin rash or itching.

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

4.3] Place In Therapy

A) Intravenous diazepam is considered an alternative choice to lorazepam for the treatment of status epilepticus [457]. Lorazepam is preferred over diazepam because of its longer duration of antiseizure effect (12 to 24 hours versus 15 to 30 minutes, respectively). Other alternative agents include intravenous phenytoin, fosphenytoin, or phenobarbital. Because of diazepam's short duration of anticonvulsant effect, a long-acting anticonvulsant (usually phenytoin) should be initiated simultaneously [458].

B) Diazepam is an effective antianxiety agent; since it is long-acting, it is preferred for sustained levels of anxiety while shorter-acting benzodiazepines are preferred for episodic anxiety. Diazepam is used preoperatively to relieve anxiety and provide sedation and light anesthesia.

C) An emulsified formulation of diazepam (Dizac(R)) is available for intravenous use only. Its duration of effect and quality of sedation has been shown to be similar to midazolam [459]. It may also produce less phlebitis than diazepam with propylene glycol [10]. One institution estimated a \$50,000 cost savings per year by substituting emulsified diazepam for midazolam for providing conscious sedation during upper and lower endoscopic procedures [459].

D) Diazepam is also useful in managing acute alcohol withdrawal symptoms and skeletal muscle spasticity; oxazepam is generally preferred over diazepam in alcohol withdrawal due to its lack of accumulation in patients with hepatic disease.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Diazepam is thought to specifically interfere with interneuronal transmission. Polysynaptic spindle reflexes are inhibited producing skeletal muscle relaxation. Tranquilization is achieved by inhibition of the limbic system [426] [409].

2) The mechanism of action of the benzodiazepines has not been fully elucidated in humans. The most promising hypothesis involves GABA transmission. GABA is a major inhibitory transmitter in the CNS. Benzodiazepines exert their pharmacological effect at the site of the GABA synapse, increasing the affinity of the receptor for GABA, thus reducing GABA turnover. Specific benzodiazepine receptors have been identified in the rat brain located in proximity to dense areas of GABA receptors, primarily in the frontal and occipital cortex [427] [428].

3) It is speculated that an endogenous protein ligand exists which normally binds to the benzodiazepine receptor and serves to produce anxiety for survival purposes. This endogenous ligand also may serve as a natural inhibitor for the regulatory site of GABA receptors. When benzodiazepines occupy the sites, the affinity of GABA receptors is increased. When the natural ligand occupies the site, GABA affinity is decreased [429]. The most recent evidence indicates that if an endogenous ligand does exist, it is most likely a benzodiazepine-like compound (agonist) with an indolic structure [430].

4)) Increased **GABA** activity can explain most of the pharmacologic effects of benzodiazepines. Increased presynaptic inhibition at the spinal level may be one site of skeletal muscle relaxation. 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 [431].

B)) REVIEW ARTICLES

- 1)) A review on **status epilepticus**, including pharmacologic therapy, has been published [391].
- 2)) The status of benzodiazepine derivatives in anxiety, depression and mixed anxiety depression, sleep disorders, alcohol withdrawal, **musculoskeletal disorders**, **anesthesia**, and surgery, as well as pharmacokinetic differences and adverse drug reactions have been reviewed [432] [433].
- 3)) Pharmacokinetic considerations of the use of benzodiazepines during pregnancy and labor were reviewed [434].
- 4)) The advantages of **diazepam** and other benzodiazepines administered orally as premedicants were reviewed [435].

4.5] Therapeutic Uses

4.5.A] **Alcohol withdrawal syndrome**

FDA Labeled Indication

1)) Overview

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

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

2)) Summary:

Indicated for use in the symptomatic relief of acute agitation, tremor, impending or **acute delirium** tremens, and hallucinations in acute alcohol withdrawal [1] [2] [3]

Benzodiazepines are the drug class of choice to treat acute alcohol withdrawal

3)) Adult:

a)) Benzodiazepines are useful in reducing withdrawal severity, incidence of **delirium**, and seizures [4]. Therapy should be individualized based on withdrawal severity. Some clinicians prefer **diazepam** because its longer duration of action which results in a smoother withdrawal [5] [6] [7].

4.5.B] **Anxiety**

FDA Labeled Indication

1)) Overview

FDA Approval: Adult, yes; **Pediatric, yes (6 months and older (oral))**

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

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

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

2) Summary:

Indicated for the symptomatic relief of anxiety and tension associated with anxiety disorders, [transient situational disturbances](#), and functional or organic disorders

3) Adult:

a) The recommended dose of [diazepam](#) is 2 to 10 milligrams given 2 to 4 times daily [8]. [Diazepam](#), in daily doses of 5 to 60 milligrams, remained effective for the treatment of anxiety for several years [11] [12] [13] [Diazepam](#) is superior to placebo in the relief of anxiety [14] [15]. However, one study [16] did not find any statistically significant difference between [diazepam](#) and placebo-treated patients after the first week of therapy.

b) A double-blind, crossover study of 11 patients found that [diazepam](#) 9 to 15 milligrams once a day produced significant improvement over placebo in anxious patients according to Hamilton Anxiety Scale, Psychiatrist's Global Status & Global Change Ratings, [Symptom Checklist](#) Anxiety and Somatization Scale, and Profile of Mood States Anxiety Scale [14].

c) In a double-blind study of 228 patients, [diazepam](#) 2 milligrams three times a day and 4 milligrams at bedtime produced more clinical improvement in anxious patients than did placebo [15].

4.5.C) Benzodiazepine withdrawal

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:

[Diazepam](#) substitution may ease the withdrawal of other benzodiazepines due to its relatively long half-life

[Diazepam](#) has been used to relief symptoms of [ZOLPIDEM WITHDRAWAL](#)

3) Adult:

a) A 46-year-old man, with a history of [polysubstance abuse](#) since a teenager, developed tolerance and dependence to [ZOLPIDEM](#), prescribed for stress-related insomnia 2 years earlier. For the first 18 months, the patient reported taking 5 to 10 milligrams (mg) at bedtime. After a few months, he began taking 1.25 to 2.5 mg in the evening and then 5 mg several times during the day to decrease anxiety, with an estimate of 400 mg daily. Furthermore, several months prior to hospital admission, he began taking [lorazepam](#) 1 mg every 8 hours, consuming several tablets a day, up to 20 tablets over

one weekend. He tapered the [lorazepam](#) one month prior to hospital admission. Upon admission, he presented with tremors, sweats, chills, shakiness, and headache. He received a 7-day detoxification protocol of [diazepam](#) (day 1, 10 mg every 4 hours for 1 day; day 2, 10 mg every 6 hours for 1 day; day 3, 5 mg every 6 hours for 1 day; day 4, 2 mg every 6 hours for 1 day, then every 8 hours for 1 day, followed by every 12 hours for 1 day and finally every 24 hours for 1 day). His anxiety was managed with [nefazodone](#) 600 mg divided throughout the day; although, he reports 3 to 4 hours of insomnia nightly [31].

b) An effective method of [diazepam](#) administration for detoxification of benzodiazepine abusers was presented [32]. Twenty-three patients abusing high doses of benzodiazepines were administered a loading dose of [diazepam](#) equal to 40% of the reported daily consumption of benzodiazepine which was a median of 150 milligrams [diazepam](#) equivalent; range, 40 to 500 milligrams. The [diazepam](#) loading dose was based on the following [diazepam](#) equivalents: [diazepam](#) 5 milligrams was equal to [oxazepam](#) 30 milligrams, [chlordiazepoxide](#) 25 milligrams, [flurazepam](#) 15 milligrams, [triazolam](#) 0.5 milligrams, [lorazepam](#) 1 milligrams, [clorazepate](#) 3.75 milligrams and [alprazolam](#) 0.25 milligrams. This loading dose was followed by a reduction in daily dose by 12% (range 8% to 20%). Seven patients withdrew from the study, enabling evaluation in 17 patients. Sixteen of these patients were detoxified successfully in the hospital without complications. These data suggest that gradual reduction of [diazepam](#) is an effective and safe method for detoxifying high dose benzodiazepine abusers.

c) [Alprazolam](#) withdrawal [delirium](#) was unresponsive to [diazepam](#) administration (40 milligrams over 14 hours) in one case [33].

4.5.D] [Eclampsia](#) - Seizure

1) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

2) Summary:

Useful when magnesium sulfate is not available

3) Adult:

a) Physicians at the Eduardo Mondlane University in Mozambique reported using rectal [diazepam](#) to successfully control eclamptic convulsions when vein access is impossible and magnesium sulfate is not available [35]. An intravenous preparation of [diazepam](#) 20 milligrams (mg) in a 10 milliliter syringe is used. The needle is removed and the barrel is lubricated. Half of the syringe is inserted into the rectum and the contents discharged. With syringe left in place, the buttocks is held together for 10 minutes. An additional 10 mg is instilled if seizures are not controlled within 10 minutes. Depending on clinical response the 10 mg rectal dose is repeated every hour.

4.5.E] [Febrile seizure](#)

1) Overview

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

Efficacy: Pediatric, Evidence is inconclusive

Recommendation: **Pediatric, Class IIb**

Strength of Evidence: Pediatric, Category B

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

2) Summary:

The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-term therapy with both daily use of **phenobarbital**, **primidone**, or **valproic acid** and intermittent therapy with oral **diazepam** in children age 6 months to 5 years with 1 or more **simple febrile seizures** even though there is evidence that both are effective in reducing the risk of recurrence [42]

Prophylactic treatment of **febrile seizures** is controversial [43] [44] [45] [46] [47] [48] [49]

3) Pediatric:

a) The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-term therapy with both daily use of **phenobarbital**, **primidone**, or **valproic acid** and intermittent therapy with oral **diazepam** in children age 6 months to 5 years with 1 or more **simple febrile seizures** even though there is evidence that both are effective in reducing the risk of recurrence [42]. However, in the event of severe parental anxiety due to **febrile seizures**, intermittent oral **diazepam** 0.35 milligrams/kilograms (mg/kg) at each episode of fever higher than 38 degrees Celsius, then every 8 hours for 48 hours or until afebrile for 24 hours may be given to the child based on studies that showed some anticonvulsants do decrease the recurrences of **febrile seizures**, and oral **diazepam** is easy and safe to give to children. Further, the associated side effects (ataxia, lethargy, or irritability) are usually mild and reversible [42] [50]. The rationale behind the lack of recommendation is because the number of children who have **febrile seizures** in the first few years of life is extremely high but the associated risks are benign, and there are no negative long-term effects in these children identified up to date. With the exception of the high rate of recurrence, **febrile seizures** are not harmful, they do not cause a decline in IQ nor behavioral abnormalities, and do not significantly increase the risk for development of future **epilepsy**. The use of anticonvulsants has high potential for adverse effects and they have not demonstrated improvement in children's long-term outcomes. Adverse effects of **anticonvulsant therapy** include: rare fatal **hepatotoxicity**, especially children less than 2 years of age who are also at greater risk of **febrile seizures**, **thrombocytopenia**, weight loss, weight gain, gastrointestinal disturbances, and **pancreatitis** with **valproic acid**; hyperactivity, irritability, lethargy, and sleep disturbances with **phenobarbital** and **primidone**; lethargy, drowsiness and ataxia for intermittent **diazepam** as well as the risk of masking an evolving central **nervous system infection**, such as **meningitis**. Therefore, the AAP does not recommend either continuous or intermittent **anticonvulsant therapy** due to the potential toxicities associated with these agents outweigh the low risks associated with **simple febrile seizures** [42].

b) There is controversy concerning the advisability of routinely administering **diazepam** prophylactically during a febrile episode in children who have had one **febrile seizure** [43] [44] [45] [46] [47] [48] [49]. A meta-analysis of randomized, placebo-controlled trials showed that there was no difference in the risk of recurrences in children receiving intermittent **diazepam** therapy and placebo (odds ratio 0.81, p equal to 0.31) [51]. One of the concerns is that side effects such as lethargy, ataxia, and irritability may mask other illness (eg, **meningitis**). Another area of disagreement is whether or not **febrile seizures** result in permanent damage. Alleviation of parental anxiety is a common justification for use of prophylactic **diazepam** therapy, but there is frequent lack of parental compliance

in administering the drug. Education and reassurance are recommended for the parents of a child who has had one [febrile seizure](#) [49].

c) There were no benefits or adverse effects associated with [febrile seizure](#) prophylaxis using rectal [diazepam](#) in the report of a 12-year follow-up study of 289 children [52]. In early childhood the children had been randomized to either [diazepam](#) at occurrence of fever or [diazepam](#) treatment only on seizure recurrence after an initial simple or [complex febrile seizure](#). Although the recurrence rate at 18 months was significantly lower in the prophylaxis group (12% vs 38%), the long term outcome was similar for both groups. Scholastic achievement, [epilepsy](#) occurrence, neurological, motor, intellectual, and cognitive skills were assessed. The authors concluded that, with the exception of children with many or long-lasting recurrences of seizures, prophylaxis of [febrile seizures](#) may be unwarranted.

d) Administration of [diazepam](#) rectally by enema was reported effective in the prophylaxis of [FEBRILE SEIZURES](#) in a controlled study [52]. A total of 289 consecutive children with their first [febrile seizure](#) were randomized to receive [diazepam](#) or no prophylaxis; diazepam-treated children (152) received 5 milligrams rectally (under 3 years of age) or 7.5 milligrams rectally (3 years or older) at home every 12 hours, whenever the temperature was 38.5 degrees Centigrade or greater, for 18 months. Control children (137) received no prophylaxis but were given [diazepam](#) rectally for new episodes of seizures. During short-term prophylaxis, a mean of 5 doses of [diazepam](#) per child per year, resulted in effective seizure control. The 18-month recurrence rate was reduced from 39% to 12%; total number of recurrences were reduced from 77 to 23, and long-lasting recurrences were reduced from 5% to 0.7%. The risk of developing subsequent [epilepsy](#) within the first 2 years was similar (3%) in treated and untreated patients; the risk was relatively high following the occurrence of [complex febrile seizures](#) (20%) or seizures associated with severe interictal EEG abnormalities (50%), but low after simple [febrile convulsions](#) (none of 230 children). The author recommends short-term prophylaxis with [diazepam](#) in children following simple seizures, despite the favorable prognosis in this group, as well as for more [complex febrile seizures](#).

4.5.F] [Opioid withdrawal](#)

See Drug Consult reference: [DRUG THERAPY OF OPIOID WITHDRAWAL](#)

4.5.G] [Poisoning by chloroquine](#)

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:

Used as adjunctive therapy in [chloroquine poisoning](#)

3) Adult:

a) A higher survival rate was reported with [diazepam](#) and [epinephrine](#) administration, in combination with immediate mechanical ventilation, for the treatment of [chloroquine poisoning](#) [34]. Eleven patients who had ingested more than 5 grams [chloroquine](#) were treated prospectively, with combined treatment

being initiated at home; results from this prospective group compared to a retrospective group of 11 patients who had ingested more than 5 grams [chloroquine](#) (control group). Ten of 11 patients treated prospectively survived as compared to 1 of 11 control patients. [Epinephrine](#) was given in doses of 0.25 micrograms/kilogram initially via a motor-driven syringe-type pump, followed by 0.25 micrograms/kilogram/minute until a systolic arterial pressure of greater than 100 mmHg was achieved; mechanical ventilation was instituted following [induction of anesthesia](#) with intravenous (IV) [thiopental](#) and intubation; [diazepam](#) 2 milligrams/kilogram was given via a motor-driven syringe-type pump (2 IV lines containing 5% [dextrose](#) were utilized for administration of [diazepam](#) and [epinephrine](#)).

4.5.H] [Premedication for anesthetic procedure](#)

See Drug Consult reference: PEDIATRIC SEDATION REGIMENS

4.5.I] [Sedation, Premedication before surgery, endoscopic procedures and cardioversion](#)

FDA Labeled Indication

1) Overview

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

Efficacy: Adult, Effective; Pediatric, Effective

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:

Useful as a premedication for relief of anxiety and tension in patients who are to undergo surgical procedures [1]

Useful as an adjunct prior to [endoscopic procedures](#) or [cardioversion](#) for relief of apprehension, anxiety, or acute stress, and to diminish recall of the procedure [1]

3) Adult:

a) Preoperative anxiety

1) [Diazepam](#) 10 milligrams was not effective in reducing preoperative anxiety in a placebo-controlled, double-blind study in 30 women undergoing [cholecystectomy](#) [25]. [Diazepam](#) was given orally to 17 patients and placebo to 13 patients. Variables measured before and after treatment included heart rate, systolic and diastolic arterial pressures, and plasma levels of adrenaline, noradrenaline, cortisol, and [dopamine](#) beta-hydroxylase. The Hamilton test for anxiety and a visual analogue scale were also used. An increase in systolic arterial pressure in the placebo group was the only significantly changed parameter (p less than 0.05). [Diazepam](#) did not affect the biochemical, behavioral, or subjective measures of anxiety.

b) [Endoscopic procedures](#)

1) In a randomized, double-blind study, [midazolam](#) and emulsified [diazepam](#) produced a similar quality of conscious sedation (p greater than 0.05) during [endoscopic procedures](#) [26]. Dosed for adequate sedation, patients received either [midazolam](#) (n=100), mean dose 10.5 milligrams (mg), or emulsified [diazepam](#) (n=111), mean dose 3.8 mg. There was no difference

in time to adequate sedation, recovery time, requirement for reversal agents, oxygen needed, or [phlebitis](#) (all p greater than 0.05). Using emulsified [diazepam](#) instead of [midazolam](#) saved the institution approximately 50%.

c) Cardioversion

1) [Diazepam](#) and [midazolam](#) were both effective sedatives for patients requiring elective day-case [CARDIOVERSION](#) of atrial [tachyarrhythmias](#). Patients requiring [cardioversion](#) were randomized to receive either intravenous (IV) boluses of [diazepam](#) (5 to 10 milligrams (mg) every minute to a maximum of 70 mg) or [midazolam](#) (5 mg followed by 1 to 2 mg every minute to a maximum of 30 mg) for sedation. Patients, but not investigators, were blinded as to the therapy received. The mean dose of [diazepam](#) (n=70) and [midazolam](#) (n=71) was 28.1 +/- 12 mg and 12.5 +/- 5 mg, respectively. Adequate sedation was achieved in 61 of 70 (87%) patients receiving [diazepam](#) and 63 of 71 (89%) patients receiving [midazolam](#). Adverse events occurred in 23% of patients receiving [midazolam](#) (hypotension (20%), oxygen desaturation (3%) and in 9% of patients receiving [diazepam](#) (hypotension (7%), additional analgesia required (6%); (p=0.14). Sedation time was significantly reduced with [midazolam](#) (5 +/- 3.4 minutes) compared with [diazepam](#) (6.5 +/- 3.4 min, p=0.0016). Time to awake after sedation was significant increased with [midazolam](#) (77 +/- 46 min) compared to [diazepam](#) (39 +/- 24 min, p less than 0.0001). Thirty-four percent of patients receiving [diazepam](#), reported unsteadiness (48%), tiredness (48%), and light-headedness (8%) as most common after-effects, while 32% of patients receiving [midazolam](#) reported tiredness (57%), light-headedness (26%), and drowsiness (13%) [27].

2) Physician-administered [diazepam](#) provided sufficient sedation for performance of [cardioversion](#), without the need for general [anesthesia](#). One hundred forty one patients with [atrial fibrillation](#) or [atrial flutter](#) were sedated by one physician and one nurse with intravenous [diazepam](#), 5 to 10 milligrams (mg), with further 5 to 10 mg aliquots each minute until adequate sedation, characterized by somnolence and loss of the eyelid reflexes, was achieved. Direct current shock was applied. [Cardioversion](#) was successful in 82% of the patients. The dose of [diazepam](#) ranged from 5 to 100 mg and was correlated inversely with age. Men required more than women. [Diazepam](#) was adequate in 97% of patients, with only 4 patients (all male) requiring additional sedation or analgesia. [Respiratory depression](#), which responded rapidly to administration of [flumazenil](#), occurred in only 2 patients (both women). No patient required assisted ventilation. No patient required an anesthetist. There were no instances of sustained [ventricular arrhythmia](#) or hypotension. No patient recalled any pain. Sedation by physician with [diazepam](#) is cost- effective and facilitates more prompt delivery of [cardioversion](#), because scheduling with an anesthetist is unnecessary [28].

4) Pediatric:

a) Rectal administration of [diazepam](#) as a solution has been used as pre-operative medication in children [29].

4.5.J] Seizure, Refractory, increased frequency

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes ((rectal gel)); [Pediatric, yes \(2 years and older \(rectal gel\)\)](#)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

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

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

2) Summary:

Indicated to control acute repetitive seizures

Home use of [diazepam](#) rectal gel is effective in decreasing emergency department visits by aborting seizure activity [36]

3) Adult:

a) A [diazepam](#) rectal gel formulation is indicated in the management of patients with [epilepsy](#) (partial onset or generalized convulsive seizures) on stable regimens of anticonvulsant medications who require intermittent use of [diazepam](#) to control bouts or clusters of increased seizure activity [36]. Patients should be identified jointly by their caregivers and physicians as suffering intermittent and periodic episodes of markedly increased seizure activity, sometimes heralded by non-convulsive symptoms, that for the individual patient are characteristic and deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. Although these clusters or bouts of seizures may differ among patients, for any individual patient the clusters of seizure activity should be distinguishable from other seizures suffered by the patient.

b) [Diazepam](#) rectal gel was effective and safe for the treatment of acute repetitive seizures outside the hospital [37]. In a double-blind study, patients were randomized to receive either [diazepam](#) rectal gel (n=45) or placebo (n=46). Doses ranged from 0.2 to 0.5 milligrams/kilogram (mg/kg) based on age. Children (2 to 14 years old) received 1 dose at the onset of seizures and another after 4 hours. Adults (15 to 60 years old) received 1 dose at onset, and 2 more doses at 4 and 12 hours after onset. The median total dose of [diazepam](#) was 20 mg for the 25 children and 37.5 mg for the 20 adults. Treatment was administered by a trained caregiver. [Diazepam](#) was significantly more effective than placebo for reducing seizure frequency (p less than 0.001 for children, p less than 0.02 for adults). Also the time to the first seizure recurrence was significantly longer in the [diazepam](#) group than in the placebo group (p less than 0.001). Somnolence was the most frequently reported adverse event; [respiratory depression](#) was not reported. Educated care givers were able to safely administer the [diazepam](#) rectally.

c) [Diazepam](#) rectal gel decreased median seizure frequency over a 12-hour observation period during a single-dose study. In a double-blind trial, patients were randomized to receive either [diazepam](#) rectal gel (n=56) or placebo (n=58) administered as a single dose (Cereghino et al, 1998). Target doses of [diazepam](#) were calculated based on patient age and weight. Mean patient age was 16.2 years and the maximal patient weight allowed was 111 kilograms. During the 12-hour observation period, patients treated with [diazepam](#) demonstrated a significantly lower median seizure frequency than those treated with placebo (0.0 versus 2.0, p=0.029) and a greater proportion remained seizure free (55% versus 34%, p=0.031). In addition, the mean caregiver and investigator global assessment scores were significantly higher in the diazepam-treated group. Somnolence was a common adverse event but no [respiratory depression](#) was reported.

4) Pediatric:

a) In a study combining the results of 2 prospective, double-blind, placebo-controlled trials, rectal [diazepam](#) gel was found to be more effective than placebo in the treatment of acute repetitive seizures in children ages 2 to 17 years (Kriel et al, 1999). Patients were randomized to receive either [diazepam](#)

(n=96) or placebo (n=89) in targeted doses of 0.5 milligrams/kilogram (mg/kg) for ages 2 to 5 years, 0.3 mg/kg for ages 6 to 11 years, and 0.2 mg/kg for those ages 12 years or older. Patients were observed for seizures and adverse effects for 12 hours after administration of the dose. Children in the [diazepam](#) group exhibited a significantly greater reduction in median seizure frequency when compared to placebo (0 versus 0.25 seizures per hour, $p=0.001$) and a longer time to the next seizure ($p=0.0002$). In addition, a greater proportion of children treated with [diazepam](#) remained seizure-free during the 12 hour observation period (59% versus 31%, $p=0.001$). Somnolence occurred at an increased frequency in the [diazepam](#) group when compared to the placebo group (25% versus 7.7%, $p=0.01$), however there was no significant difference in median [respiratory depression](#).

b) Home use of rectally administered [diazepam](#) (0.3 to 0.5 mg/kg doses) was found to be a safe and cost effective treatment for pediatric cluster or prolonged seizures [38]. Seizures were controlled in 85% of patients. Emergency room visits decreased and an improved quality of life, due to reduced family stress, was reported by 58% of families.

c) Use of rectal [diazepam](#) gel in the home management of prolonged or repetitive seizures is effective in aborting seizure activity, often avoiding an emergency department visit. This prospectively recruited study group included 38 children with a mean age of 4.2 years (range: 6 months to 12.3-years-old). There were 14 children (37%) with [complex febrile seizures](#), and 24 with [epilepsy](#) (n=22) or a single seizure (n=2). There were 23 (61%) children with a history of prolonged seizures and 15 (39%) with a history of repetitive seizures. In the 6 months before study enrollment, 33 (86%) had at least one emergency department visit. During the 6 months after study entry, 12 children had one or more prolonged or repetitive seizures that met the criteria for administration of [diazepam](#) rectal gel. The rectal [diazepam](#) gel was administered to 8 children on 19 occasions. In 16 (84%) of the episodes, seizures stopped and no emergency department visit was required. The three remaining episodes occurred in two children with very difficult to treat [epilepsy](#) and both were taken to the emergency department. One of the children had six prolonged episodes throughout the 6 month study period and the [diazepam](#) rectal gel prevented an emergency department visit in four cases. There were seven occasions in six children when rectal [diazepam](#) gel was not given and children were taken to the emergency department on six of these occasions. Reasons for not using the [diazepam](#) rectal gel included: family had not refilled prescription, parental insecurities with seizure identification and when to administer and family decided not to give medication and took child to the emergency department. The parental stress index was also assessed at baseline with 14 (37%) of parents indicating a moderate stress level and 7 (18%) with a high stress level. After 6 months there were significant improvements found in parental stress, 14 (37%) of the parents scored in the mild stress range and 7 (18%) in the moderate range (p less than 0.001). Aside from the expected sedation with [diazepam](#) rectal gel, there were no other adverse events reported in any of the children [39].

4.5.K] Seizure; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, yes (6 months and older (oral); greater than 30 days (injectable); 2 years and older (rectal))

Efficacy: Adult, Effective; Pediatric, Effective

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:

May be used adjunctively in convulsive disorders

Not proven useful as the sole therapy

Effectiveness of [diazepam](#) in long-term use (greater than 4 months) has not been assessed

3) Adult:

a) [Diazepam](#) (5 milligrams intravenously) was efficacious in reducing seizures secondary to contrast media in patients with known or suspected [brain metastases](#) undergoing cerebral [computed tomography](#). [Diazepam](#) 5 milligrams was administered prior to contrast injection [20].

4) Pediatric:

a) Hemodialysis-associated seizures (HAS) were apparently eliminated by [diazepam](#) treatment administered 30 minutes prior to dialysis sessions. All of 9 children who had experienced HAS were treated with oral [phenobarbital](#) (PB) 5 milligrams per kilogram (mg/kg) per day. In addition, 4 of the children received oral [diazepam](#) 0.5 mg/kg 30 minutes before each [hemodialysis](#) session. During 6 months' observation, those receiving [diazepam](#) experienced no seizures, while those receiving only PB continued to have seizures. [Diazepam](#), in contrast to PB, is non-dialyzable [21].

b) Rectal [diazepam](#) has been efficacious in the treatment of pediatric seizures [22] [23]. Rectal administration of [diazepam](#) solution for injection, 20 milligrams, significantly reduced the frequency of interictal spikes in the EEG in a group of 10 epileptic patients [24].

4.5.LJ Skeletal muscle spasm; Adjunct

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(6 months and older \(oral\)\)](#)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

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

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

2) Summary:

Indicated as adjunct therapy for the relief of skeletal muscle spasms due to reflex spasm to local pathology, [upper motor neuron disorders](#), athetosis, and [stiff-man syndrome](#) [1] [2] [3]

Also used to relieve spasticity found with [multiple sclerosis and spinal cord](#) lesions

3) Adult:

a) [Diazepam](#) is indicated as adjunct therapy for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as [inflammation of the muscles](#) or [joints](#), or secondary to trauma); spasticity caused by [upper motor neuron disorders](#) (such as [cerebral palsy](#) and [paraplegia](#)); athetosis; and [stiff-man syndrome](#) (De Lee Rockwood, 1980) [17]. It has also been used to relieve spasticity found with [MULTIPLE SCLEROSIS and SPINAL CORD LESIONS](#). Tolerance to this action of [diazepam](#) may develop after prolonged use and may necessitate drug holidays or alternate drug therapy. Normal adult

dosage is 2 to 10 milligrams orally four times a day. Intravenous administration may be used in severe spasticity.

4.5.M] Skeletal muscle spasm - Tetanus

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes ((injectable)); Pediatric, yes (greater than 30 days (injectable))

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIb; Pediatric, Class IIb

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

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

2) Summary:

Successfully used in cases of patients with muscle rigidity and spasms associated with [tetanus](#)

3) Adult:

a) [Diazepam](#) infusion was used successfully in a patient with muscle rigidity and spasms associated with [tetanus](#) [30]. An intravenous infusion of [diazepam](#) at 10 milligrams per hour was started on the fifth hospital day with opisthotonos resolving within 24 hours and facial grimace resolved by day 7. A beneficial response was observed with [diazepam](#) concentrations of 500 nanograms/milliliter or greater.

b) [Diazepam](#) infusion was used successfully in the treatment of seizures associated with [tetanus](#) in a 31-year-old male [18]. It was found that [diazepam](#) can be used successfully as an intravenous infusion (in lactated Ringers) in doses ranging from 5 milligrams/hour to 15 milligrams/hour, then gradually tapered and eventually replaced with oral [diazepam](#). An initial dose of 5 milligrams/hour of [diazepam](#) was administered via infusion pump using a dilution of 100 milligrams in 500 milliliters of lactated Ringers injection (Hartman's solution).

4.5.N] Spasticity

See Drug Consult reference: SPASTICITY - DRUG THERAPY

4.5.O] Status epilepticus

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes ((injectable only)); Pediatric, yes (30 days and older (injectable only))

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:

Indicated as an adjunct agent for the initial control of [status epilepticus](#) and severe recurrent convulsive seizures [1]

3) Adult:

a) Intravenous [diazepam](#) is indicated for the initial control of [status epilepticus](#) and severe recurrent convulsive seizures [54] [55] [56]. It is given to temporarily control the seizures while a loading dose of a long-acting antiepileptic is being administered [57] [58] [59]. Usual adult dosage is 5 to 10 milligrams intravenously, given at a rate of no greater than 5 milligrams/minute.

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) [60]. In a multicenter, 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) Pediatric:

a) In children five years and older the dose is 1 milligram (mg) every 2 to 5 minutes as needed up to 10 mg. In children less than five years and older than 30 days, doses of 0.2 to 0.5 mg every 2 to 5 minutes as needed up to 5 mg are recommended [1] [57] [59].

b) In several studies, intravenous (IV) [diazepam](#) has been used in doses ranging from 0.1 milligram/kilogram (mg/kg) to 0.5 mg/kg in pediatric patients with varying degrees of success [61] [62]. In a retrospective chart review, [diazepam](#) and [lorazepam](#) achieved similar control of [status epilepticus](#) in children aged 2 weeks to 18 years (n=193), with mean effective IV doses of 0.38 mg/kg (standard deviation (SD), 0.21; range, 0.09 to 0.71 mg/kg) and 0.11 mg/kg (SD, 0.05; range, 0.03 to 0.22 mg/kg), respectively [63]. In one comparative study, a mean IV [diazepam](#) dose of 0.32 mg/kg (range, 0.15 to 0.5 mg/kg) was as effective as [lorazepam](#) (mean dose 0.13 mg/kg; range, 0.05 to 0.2 mg/kg) in controlling [status epilepticus](#) in children aged 0.5 years to 11 years (n=48) [64]. The American Academy of Pediatrics Committee on Drugs recommends an IV [diazepam](#) dose of 0.1 mg/kg up to a maximum of 0.3 mg/kg every 2 minutes with a maximum of 10 mg per dose [53]. However, the manufacturer for [diazepam](#) recommends that doses not exceed 5 mg in children 30 days to 5 years of age and 10 mg in children 5 years of age or older. The safety and efficacy of [diazepam](#) use has not been established in children less than 30 days of age [1].

c) Intravenous [diazepam](#) was reasonably effective in controlling refractory [status epilepticus](#) in a retrospective review of 57 charts of children admitted to a pediatric intensive care unit [65]. The mean age of the children was 2.8 years (1.5 to 11.5 years) and 60% had acute infections and 16% had [idiopathic epilepsy](#). A standard [diazepam](#) infusion protocol was used beginning with [diazepam](#) 0.3 milligrams/kilogram (mg/kg) for 2 doses plus intravenous [phenytoin](#) 20 mg/kg in the first 30 minutes. After 30 minutes, [diazepam](#) 0.3 mg/kg was administered with intravenous [phenobarbital](#) 20 mg/kg. Seizures were controlled in 86% of patients within an average of 40 minutes. Adverse reactions included hypotension, [respiratory depression](#) requiring ventilatory support (12%), and death (14%).

d) Rectal diazepam was as efficacious and safe as intravenous (IV) diazepam in the pre-hospital treatment of 30 pediatric status epilepticus patients in a retrospective analysis [22]. The subjects of this study were less than 18 years old and experienced either generalized tonic-clonic, clonic, or tonic seizures lasting more than 15 minutes or repetitive seizures lasting more than 15 minutes. Diazepam was given to 15 patients (IV group) at doses ranging from 2 to 10 milligrams (mg) (0.04 to 0.33 mg/kilogram (kg)), and diazepam per rectum (PR) was administered to 16 patients (PR group) at doses ranging from 2 to 7.5 mg (0.16 to 0.57 mg/kg). The mean ages were 9.1 years (IV group) and 3 years (PR group). Seizures stopped within 10 minutes of drug administration in 13/16 patients in the PR group; 4 patients had seizure recurrence before arrival at the hospital, and 2 of those 4 again stopped seizing before arrival. No patient in the PR group needed intubation for respiratory depression in the field or had significant decline in blood pressure. Eight patients experienced re-seizure; 7 of these patients were diagnosed with acute, serious underlying etiologies (eg, encephalitis, hypothyroidism, pneumococcal bacteremia). Seizures stopped within 10 minutes in all patients in the IV group, but 9/15 experienced seizure recurrence before arrival at the hospital, and 6/15 had recurring seizures. In this study, when compared with IV administration, rectal diazepam was easier to use in infants and young children, had a longer duration of action, and may have lowered the risk of respiratory depression.

e) Case reports with undiluted, rectally administered diazepam successfully terminated seizures in five pediatric (11 months to 8 years of age) status epilepticus patients [41]. Seizure abatement occurred in 1 to 3 minutes when doses of 0.5 milligrams/kilogram (mg/kg) were used. In patients administered serial doses, seizure activity stopped as the total dose approached 0.5 mg/kg. Respiratory depression was not reported in any of the five cases.

4.5.P] Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Abecarnil

4.6.A.1] Generalized anxiety disorder

a) Abecarnil was moderately efficacious when used to treat generalized anxiety disorder (GAD) in a randomized, double-blind, dose-ranging clinical trial employing diazepam or placebo as dual controls. Patients with non-depressive GAD (mean Hamilton Rating Scale for Anxiety (HRSA) score = 24.4 points) were provided short-term treatment with oral abecarnil 7.5 to 17.5 milligrams (mg)/day (dosage escalation based upon patient's perception of efficacy or tolerability) (n=102), oral diazepam 15 to 35 mg/day (n=104), or placebo (n=104). Mean daily doses at weeks one and six of the short-term study were 7 and 11.8 mg for abecarnil, 13.7 and 21 mg for diazepam, and 2.8 and 5.6 capsules of placebo. Treatment responders were offered the option of continuing double-blind treatment for up to 24 weeks (treatment end-point) if desired, followed by a 3-week taper regimen. Primary efficacy measures were the HRSA and the Clinical Global Impression Scale (CGI) of illness severity. A rapid onset of anxiolytic effect was observed in both the abecarnil and diazepam groups, accompanied by significantly greater clinical improvement in both treatment groups compared with placebo during weeks 1 through 6 (p less than 0.05 to 0.001), with reductions in HRSA scores at week 6 of 64% and 72% for abecarnil and diazepam groups, respectively, and in week 6 CGI scores of 69% and 80%, respectively. However, only diazepam maintained its statistically significant advantage over placebo at treatment end-point, possibly due in part to a rather high placebo effect (56% of placebo patients exhibiting at least moderate global improvement at end-point). Adverse events were similar among abecarnil and diazepam patients, with drowsiness and

dizziness most prevalent. Significantly more patients receiving [diazepam](#) for more than 12 weeks duration experienced adverse withdrawal events compared with either abecarnil or placebo patients on similar regimens (p less than 0.05) [655].

4.6.B] Acetophenazine

4.6.B.1] Anxiety

a) Acetophenazine was compared with [diazepam](#) in 67 depressed patients with significant anxiety. Mean daily dosages of the two drugs were 248 milligrams and 47 milligrams, respectively. Acetophenazine was noted to produce more drowsiness and restlessness while [diazepam](#) produced more ataxia. Patients with more recent onset of illness and uncomplicated depressions responded better to [diazepam](#) while those with long-standing illness or alcoholism were better treated with acetophenazine. The authors suggested that antianxiety drugs were preferred as initial treatment of anxiety with patients suffering from depression [480].

4.6.C] Alpidem

4.6.C.1] Anxiety

a) Alpidem is comparable to [diazepam](#) in the treatment of anxiety. Alpidem 50 milligrams 2 times a day was compared with [diazepam](#) 5 milligrams twice a day for 21 days. Objective testing showed a more than 50% reduction in symptoms of anxiety with both drugs; according to the Clinical Global Impression (CGI) scale at the end of the study, 67% of patients treated with alpidem and 72% of patients treated with [clorazepate](#), [diazepam](#), or [lorazepam](#) (all 3 groups together) responded to treatment (although the difference was not statistically significant). While the incidence of sedation (somnolence or drowsiness) experienced with alpidem was similar to that seen with the benzodiazepines, the incidence of fatigue and depression was much lower than that which occurred with the benzodiazepines [561].

4.6.D] Alprazolam

4.6.D.1] Alcohol withdrawal syndrome

a) [Alprazolam](#) has been demonstrated as effective as [diazepam](#) in the management of chronic alcohol withdrawal, but it offers no specific advantages [606]. The efficacy and safety of [alprazolam](#) was compared with [diazepam](#) in 46 alcoholics in double-blind fashion. Both drugs were administered randomly for 21 days beginning on the 5th day after the last drink. The mean optimal daily dose of [alprazolam](#) was 2.2 milligrams (range 1.5 to 4.5 mg/d) and [diazepam](#) 20.2 milligrams (range 15 to 45 mg/d). Based on Hamilton anxiety scores, global scores and other test procedures, both drugs produced significant clinical improvement in 95% of patients in both groups, with no significant difference between the drugs at any time. Both drugs produced frequent drowsiness and lightheadedness with the only difference in side effects being a higher incidence of depression in patients receiving [alprazolam](#) (6 patients as compared to 1 receiving [diazepam](#)). Although the drug has been shown to be as effective as [diazepam](#) in the treatment of alcohol withdrawal, it offers no specific advantages [606].

4.6.D.2] Anxiety

a) Controlled studies have reported that [alprazolam](#) is at least as effective as [diazepam](#) in the treatment of outpatients with anxiety [607] [608] [609] [610] [611]. The incidence of sedation was lower with alprazolam in some reports (Rickels, 1983a) [609] [610].

b) [Alprazolam](#) 1.5 to 3 milligrams daily was at least as effective as [diazepam](#) 15 to 30 milligrams daily as an anxiolytic in a controlled study involving 46 outpatients with moderate to severe anxiety.

[Alprazolam](#) demonstrated antidepressant activity in [neurotic depression](#), whereas no antidepressant effect was observed with [diazepam](#) [607].

c) [Alprazolam](#) was compared with [diazepam](#) and placebo in 235 outpatients with anxiety in a 28-day double-blind study [610]. [Alprazolam](#) in mean doses of 1.5 milligrams orally daily was reported as effective as [diazepam](#) 18.6 milligrams (mean) orally daily in this study. [Alprazolam](#) was reported to produce a markedly lower incidence of side effects than [diazepam](#) or placebo, particularly drowsiness. Depression and lightheadedness was reported with both drugs, although less frequently in patients receiving [alprazolam](#). In this study, a detailed description of side effects was not provided, making evaluation of these 2 drugs difficult.

4.6.D.3] [Panic disorder](#)

a) The tolerability and efficacy of [diazepam](#) and [alprazolam](#) was compared over 8 weeks using a double-blind, placebo controlled study with 24 subjects. They found that on all measures of efficacy both agents showed equally favorable results. Despite some sedation during the early part of the trials, both drugs were tolerated well [612].

4.6.E] [Amobarbital](#)

1) Efficacy

a) [Amobarbital](#) improved quality of sleep while [diazepam](#) improved anxiety in a comparison of clinical and psychobiological effects [491]. [Amobarbital](#) 100 milligrams was compared with [diazepam](#) 5 milligrams in 24 anxious inpatients on a flexible dosing regimen. [Diazepam](#) significantly improved subjective anxiety whereas [amobarbital](#) improved only the quality of sleep on self-rating scales. [Amobarbital](#) produced significant reductions in motor task performance versus placebo, but performance with [diazepam](#) was impaired to an even greater extent.

b) [Amobarbital](#) has also been used for reduction of anxiety in postcoronary patients. While [amobarbital](#) was as effective in reducing anxiety as [diazepam](#) and [chlordiazepoxide](#), there was a significantly higher incidence of side effects seen with [amobarbital](#) [492] [493].

4.6.F] [Baclofen](#)

4.6.F.1] [Multiple sclerosis](#)

a) No significant differences were found between [baclofen](#) and [diazepam](#) in terms of reduction in spasticity, clonus, flexor spasms, gait, and bladder function. The clinical effects of [baclofen](#) and [diazepam](#) were compared in a double-blind trial in [multiple sclerosis](#) patients. The patients were treated with [baclofen](#) or [diazepam](#) for a period of 4 weeks, then separated by placebo period and again treated for 4 weeks in a crossover manner. The average optimal daily dose of [baclofen](#) was 61.2 milligrams (range 30 to 120 mg daily) and for [diazepam](#) 26.8 milligrams (range 10 to 40 mg daily) [633].

4.6.F.2] [Spasticity](#)

a) [Baclofen](#) 25 to 60 milligrams daily was comparable to [diazepam](#) 10 to 40 milligrams daily in the treatment of spasticity in a controlled study [631]. Side effects were less with [baclofen](#) and consisted primarily of daytime sedation. Long-term [baclofen](#) therapy (4 years) resulted in continued efficacy and no evidence of tolerance. [Baclofen](#) is suggested as preferable to [diazepam](#) due to a lower incidence of side effects and lack of withdrawal effects upon gradual discontinuation.

b) [Baclofen](#) (60 milligrams) has been shown to be effective in patients not responding to [diazepam](#) (30 to 60 milligrams daily) [632].

4.6.G] Bromazepam

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

a) Oral bromazepam 9 milligrams was reported as effective as oral [diazepam](#) 10 milligrams as a preoperative anxiolytic when given between 1.5 and 3 hours prior to surgery in women undergoing [gynecological surgery](#) [604]. Bromazepam has no advantage over [diazepam](#) as a premedicant prior to surgery, unless cost factors are in favor for bromazepam.

4.6.G.2] Anxiety

a) Several studies have reported that bromazepam is at least equivalent to [diazepam](#) in anxiolytic effects in patients with [anxiety-neuroses](#) [597] [598] [599] [600], other reports have indicated that bromazepam is superior or preferred over [diazepam](#) [601] [600]. There is some evidence that bromazepam may be more specific as an anxiolytic than [diazepam](#) [602] [599].

b) Bromazepam 18 milligrams daily was more effective than [diazepam](#) 15 milligrams daily in a placebo-controlled double-blind study in 48 anxious outpatients with a primary diagnosis of [generalized anxiety disorder](#) [601]. Both drugs were superior to placebo from 1 week onward relieving anxiety symptoms. Bromazepam was significantly more effective than [diazepam](#) with respect to the somatic anxiety factor and total score for the Hamilton Anxiety Rating Scale and the fear/anxiety factor of the Patients Self-Rating Symptom Scale. It is stressed that the use of strict diagnostic criteria, adequate sample sizes, and a 4-week study may provide increased sensitivity for the detection of subtle differences between benzodiazepines. However, doses of bromazepam utilized (6 mg three times a day) are higher than what are considered optimal by some investigators, and may have accounted for differences in efficacy.

c) Oral bromazepam 18 milligrams daily was reported superior to oral [diazepam](#) 15 milligrams daily in the treatment of generalized anxiety [603]. However, bromazepam was associated with a greater incidence of side effects and a trend toward a greater increase in anxiety following withdrawal as compared with [diazepam](#).

d) In a double-blind, randomized trial of 120 patients, the UK Royal College of General Practitioners determined bromazepam efficacy to be equal to that of [diazepam](#) for the treatment of mild to moderate anxiety [600]. The treatment protocol consisted of 3 treatment arms, bromazepam 3 milligrams, bromazepam 6 milligrams, and [diazepam](#) 5 milligrams, all doses were given 3 times daily for a period of 14 days. Severity was judged by utilization of the Hamilton anxiety rating scale, physicians evaluated patient response at the end of 14 days and recorded the results using a global rating scale. Significant and similar results were obtained for all treatment arms; however, the lower bromazepam regimen was associated with the least unwanted effects and best dosage compliance.

4.6.G.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 [605].

4.6.H] Brotizolam

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

a) Prior to minor [gynecological surgery](#), 70 patients were randomized to receive either sublingual brotizolam or oral [diazepam](#) as a pre-medicant. Dosage of each drug was modified based on weight (0.25 milligram brotizolam or 5 milligrams [diazepam](#) for patients less than 50 kg; 0.5 mg brotizolam or 10 mg [diazepam](#) for patients greater than 50 kg). Assessments of coma scores, auditory response time and anxiety scores were similar between groups at all time periods with one exception: one hour after premedication, coma scores were significantly longer in the brotizolam group. Patient satisfaction scores were significantly higher in the brotizolam group [500].

4.6.I] [Buspirone](#)

4.6.I.1] Anxiety

a) SUMMARY: [BusPIRone](#) and [diazepam](#) appear to be similarly effective in the treatment of anxiety disorders. Onset of action is more rapid with [diazepam](#). [BusPIRone](#) should not be used in patients recently treated for generalized anxiety with benzodiazepines. On a milligram-milligram basis, oral [busPIRone](#) appears to be equivalent in efficacy to oral [diazepam](#) in the treatment of anxiety disorders, while producing a lower incidence of CNS side effects and [impairment of psychomotor skills](#) [501] [502] [503] [504] [505] [506] [507] [508].

b) The superiority of [diazepam](#) over [busPIRone](#) was reported in the treatment of chronic anxiety in a placebo-controlled study involving 33 outpatients [509]. Oral [diazepam](#) 20 milligrams daily (mean) was superior to [busPIRone](#) in the same dose, and to placebo, on most clinical rating scales; expected EEG changes were observed with [diazepam](#) but not with [busPIRone](#). There were 9 dropouts from the trial, with 6 patients withdrawing due to inefficacy of [busPIRone](#). Of the 24 evaluable patients, 23 had previously received long-term benzodiazepine therapy, with 10 patients being unable to tolerate the pretrial placebo washout period (7 days). These data suggest that [busPIRone](#) is ineffective in the treatment of chronic generalized anxiety in patients who have recently received benzodiazepine therapy. It is suggested that this is related to lack of cross-tolerance between [busPIRone](#) and [diazepam](#), resulting in failure of [busPIRone](#) to suppress the benzodiazepine withdrawal syndrome. Withdrawal symptoms in this study appeared to be maximal at the time the beneficial effects of [busPIRone](#) would normally be observed, suggesting that the symptoms (resembling anxiety phenomena) were not suppressed by [busPIRone](#).

c) The efficacy of [busPIRone](#) and [diazepam](#), each in oral doses of 10 to 40 mg daily, was compared in the treatment of [generalized anxiety disorder](#) in a 4-week controlled study involving 66 outpatients [510]. [BusPIRone](#) doses were higher than those of [diazepam](#) throughout the study, with patients receiving a mean daily [busPIRone](#) dose of 16.5 milligrams, compared with 13 milligrams of [diazepam](#). The onset of efficacy was earlier with [diazepam](#) than [busPIRone](#). [Diazepam](#) was considered superior to [busPIRone](#) during the initial 2 weeks of treatment; however, both drugs were equivalent in efficacy after 4 weeks of treatment. Adverse effects were more frequent in [diazepam](#)-treated patients. The study was skewed in that significantly more patients received [busPIRone](#) than [diazepam](#) (43 versus 13), and it is unclear whether a more balanced patient sample would have altered the outcome.

d) Compared with [diazepam](#), there is some evidence that oral [busPIRone](#) may be more effective in females, as compared to males. In addition, [diazepam](#) may be more effective in reducing somatic symptoms, while [busPIRone](#) might be more effective in reducing symptoms associated with cognitive and interpersonal problems [505]; however, more studies are required to delineate these differences.

e) [BusPIRone](#) (average 16.5 milligrams daily orally) was compared with [diazepam](#) (15 milligrams daily orally) for the treatment of mixed anxiety and depression in a double-blind trial. Both drugs were similarly efficacious in relieving symptoms of both anxiety and depression in 100 patients; however, [busPIRone](#) showed benefits over [diazepam](#) in improving impaired cognition and confusion. Side effects (sedation, drowsiness) were significantly less with [busPIRone](#) [504].

4.6.J] [Butorphanol](#)

4.6.J.1] Sedation

a) The ease in performing endoscopic examinations and the quality of sedation was comparable in 51 patients who were treated with intravenous (IV) **diazepam** 12 milligrams (mean) or IV **butorphanol** 4.8 milligrams (mean) [499]. Both drugs provided comparable sedation in 51 patients undergoing **endoscopic procedures**.

4.6.K] Carisoprodol**4.6.K.1] Disorder of skeletal muscle**

a) Several studies have compared **diazepam** with **carisoprodol** in acute musculoskeletal conditions; however, due to deficiencies in these studies, no definite conclusions can be made as to which drug is superior to the other. One study [669] reported that **diazepam** and **carisoprodol** were equally effective (350 milligrams 4 times daily **carisoprodol** and 2.5 milligrams 4 times daily **diazepam** for 7 days). Other studies have reported the superiority of **diazepam** over **carisoprodol** in acute musculoskeletal conditions [670] [671]. However, statistical tests used in these studies were considered inappropriate by one reviewer [672]. One other report indicated the superiority of **diazepam** over **carisoprodol** in improving musculoskeletal spasm; however, **carisoprodol** was not different from **diazepam** in pain relief [673]. No statistical analysis was performed in this study.

4.6.L] Chloral Hydrate**4.6.L.1] Dental surgical procedure - Preoperative sedation**

a) Two doses of **diazepam** were comparable with **chloral** hydrate in 30 children between the ages of 20 and 48 months. In a double-blind fashion, patients received a dose of either 0.3 or 0.6 milligram/kilogram of **diazepam** during the first visit and 50 milligrams/kilogram of **chloral** hydrate on a subsequent visit. All children were restrained in a Papoose board and received 50% nitrous oxide and oxygen during treatment. **Diazepam** and **chloral** hydrate had similar sedative effects [559].

4.6.M] Chlordiazepoxide**4.6.M.1] Anxiety**

a) Several studies have indicated the superiority of **diazepam** over **chlordiazepoxide** in the management of anxiety [656] [657] [658]; (Daneman et al, 1964) [659] [660].

4.6.N] Chlormezanone**4.6.N.1] Anxiety**

a) **Chlormezanone** 400 milligrams at bedtime and **diazepam** 5 milligrams 3 times daily were equally effective in improving symptoms of anxiety and duration and quality of sleep in a double-blind multicenter trial in 44 patients with symptoms of neurotic anxiety. The author suggested that **chlormezanone** was an appropriate substitute for **diazepam** or other antianxiety drugs with the advantage of once daily dosing [661].

4.6.N.2] Migraine

a) **Diazepam** 5 milligrams and **chlormezanone** 400 milligrams had similar efficacy in 151 patients treated for acute migraine attacks. All patients received simultaneous treatment with **metoclopramide** 10 mg and **acetaminophen** 1000 mg. Patients with severe pain demonstrated significantly better treatment results

than did patients with medium- severity pain with no significant differences noted between [diazepam](#), [chlormezanone](#), or placebo. In the patients with medium-severity pain, only [chlormezanone](#) produced a significant effect [662].

4.6.O] [Chlorzoxazone](#)

4.6.O.1] Injury of muscle

a) In a double-blind, randomized study, [chlorzoxazone](#) was superior to [diazepam](#) in the relief of pain due to muscle spasm due to [musculoskeletal injury](#) [529]. Patients received either [chlorzoxazone](#) 750 milligrams or [diazepam](#) 5 milligrams 4 times daily; 24 patients assigned to each group completed the study. No physical therapy was administered to either group. [Chlorzoxazone](#) was superior to [diazepam](#) in reducing pain, tenderness, and limitation of movement. [Chlorzoxazone](#) was also superior in lack of interference with normal activities. However, other authorities have found [chlorzoxazone](#) to be inferior to [diazepam](#) in clinical treatment of muscle spasm due to [musculoskeletal injury](#) [530]

4.6.P] [Clobazam](#)

4.6.P.1] Anxiety

a) Comparative studies have indicated the similar efficacy of clobazam 30 to 80 milligrams daily and [diazepam](#) 15 to 40 milligrams daily in the treatment of anxiety [465] [466] [467] [468] [469] [470]. One study [471] reported the potential superiority of clobazam over [diazepam](#). Clobazam 20 to 80 milligrams daily was as effective as [diazepam](#) 10 to 40 milligrams daily in the treatment of anxiety and tension in the outpatient setting [472].

b) Clobazam may produce less [psychomotor impairment](#) than the therapeutically equivalent doses of [diazepam](#) [473] [474]; however, other studies have not supported these findings [475]. In general, the incidence of sedation and drowsiness is similar with [diazepam](#) and clobazam [468] [471] [472] [474] [476] [470]. In other tests of motor skills (driving tests), clobazam has produced less impairment than therapeutically equivalent doses of [diazepam](#) [473]; however, some tests have indicated performance impairment with clobazam [477]. Based on available data, it does not appear that clobazam will offer any major advantage over [diazepam](#) with regard to [psychomotor impairment](#). However, more comparative studies differentiating "sedation" and "drowsiness" from "[psychomotor impairment](#)" are needed to determine specific differences.

c) A similar incidence of sedation with clobazam (mean dose, 59 milligrams daily) and [diazepam](#) (mean dose, 25 milligrams daily) was reported [465]. Sedation occurred in 44% and 38% of [diazepam](#)- and clobazam-treated patients, respectively; sedation also occurred in 26% of placebo-treated patients. It is suggested that the occurrence of dizziness during [diazepam](#) therapy may account for differences observed in psychomotor tests between the two drugs in previous studies. Dizziness occurred in four times as many [diazepam](#)-treated patients in this report.

d) A newer anxiolytic agent, [buspirone](#), has not been associated with significant sedative effects or [impairment of psychomotor](#) function and will most likely be utilized as an alternative to [diazepam](#) and other benzodiazepines in patients unusually sensitive to these effects. Comparative studies with [buspirone](#) and clobazam may be in order to determine if clobazam will also have a role in these types of patients. However, at present, it does not appear that clobazam will replace [buspirone](#) for this indication.

4.6.Q] [Clomipramine](#)

4.6.Q.1] [Agoraphobia](#)

a) [ClomiPRAMINE](#) was significantly superior to [diazepam](#) in the treatment of 33 agoraphobic patients during a 12-week, multicentered, randomized, double-blind study [478]. The patients were diagnosed

with [agoraphobia](#) or [social phobia](#) of at least a 1-month duration. Both drugs were administered orally in low doses initially; the doses were then increased to 25 to 150 milligrams in 3 divided daily doses for [clomiPRAMINE](#) and to 10 to 30 milligrams in 3 divided daily doses of [diazepam](#). Headaches were experienced more in the [diazepam](#) group, while dry mouth and drowsiness were more prevalent in the [clomiPRAMINE](#) group. By the end of the study, [clomiPRAMINE](#) demonstrated significant improvement over [diazepam](#) in total scores for situational anxiety, interference in life-style, and accompanied travel distance on an [agoraphobia](#) inventory.

4.6.R] [Clonazepam](#)

4.6.R.1] [Status epilepticus](#)

a) Intravenous (IV) [clonazepam](#) was administered to 17 children (2 weeks to 15 years of age) in [status epilepticus](#) [613]. The initial [clonazepam](#) dose was 0.25 milligram as a bolus injection; this dose was repeated at 30-second intervals until the seizures stopped. Intravenous [diazepam](#) was used for comparison in 6 children who had further episodes of [status epilepticus](#). [Clonazepam](#) was as effective as [diazepam](#) in halting seizure activity (all 17 episodes of status were successfully stopped within 3 minutes by intravenous (IV) [clonazepam](#)) and had a longer mean duration of action ([clonazepam](#): 24.5 hours versus [diazepam](#) 8.8 hours). Although reported side effects in this study were minimal, one worker feels that [clonazepam's](#) use in status will be limited by its cardiorespiratory depressant effects [614]. There is no IV [clonazepam](#) preparation currently available.

4.6.S] [Clonidine](#)

1) Efficacy

a) [Clonidine](#) was more effective than oral [diazepam](#) in reducing hemodynamic changes associated with [TRACHEAL EXTUBATION](#) in children who underwent [general inhalation anesthesia](#). In a double-blind, control study (n=50), patients (age ranged from 4 to 10 years) were randomized to receive orally, [diazepam](#) 0.4 milligram per kilogram or [clonidine](#) 4 micrograms per kilogram orally 105 minutes before induction of [inhalation anesthesia](#). Patients in the [clonidine](#) group had less changes in heart rate and diastolic and systolic blood pressure after [tracheal extubation](#) (p less than 0.05 when compared with the [diazepam](#) group). More patients in the [diazepam](#) group experienced coughing (p less than 0.05) and no patient in either group reported having [laryngospasm](#), breath-holding, or hypoxemia [563].

4.6.T] [Clorazepate](#)

4.6.T.1] [Anxiety](#)

a) Numerous studies have indicated that [clorazepate](#) and [diazepam](#) are both effective in treating anxiety and that there are no statistically significant differences between the two agents. Isolated studies indicate that [clorazepate](#) is in certain instances more effective than [diazepam](#) but the results from most of these studies have not yet been confirmed [620]. In a study of 30 patients, [clorazepate](#) in a dose of 7.5 milligrams three times/day was less effective than [diazepam](#) according to Global, Hamilton, Wittenborn, and Zung rating scale assessments [621]. In a series of 90 patients, 32 of whom were treated with [clorazepate](#) in a dosage range of 22.5 to 37.5 milligrams/day, [clorazepate](#) response in patients with chronic anxiety or anxiety [depressive neurosis](#) was substantially better than a response to [diazepam](#) [622]. However, a vast majority of available studies indicated that both [clorazepate](#) and [diazepam](#) are significantly superior to placebo but that these studies (usually double-blind, cross-over, placebo control) have failed to demonstrate any statistically significant difference between the 2 drugs using standard measures of anxiety and tension [623] [624] [625]; (Itil, 1972) [626] [627] [628] [629] [630].

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

c) [Clorazepate](#) was less effective than either [prazepam](#) (Verstran(R)) or [diazepam](#) in treating anxiety in 60 patients (age 21 to 61 years) as assessed by the Hopkin's Symptoms check-list. However, all 3 drugs were superior to placebo. In this double-blind study, average doses given were [prazepam](#) 40 milligrams/day, [diazepam](#) 22 milligrams/day and [clorazepate](#) 29 milligrams/day for 28 days. The Hamilton Anxiety Scale showed improvement with all 3 drugs but no difference between them [630].

4.6.U] Clothiapine

4.6.U.1] Alcoholism

a) A double-blind, crossover trial compared the effect of clothiapine and [diazepam](#) in the treatment of mental symptoms in 35 chronic alcoholic patients (mean age 41.5 years). In a preliminary investigation, 9 patients were treated with clothiapine 15 milligrams (mg) three times daily and [diazepam](#) 10 mg three times daily. It was found that the dosage was too high (the subjects became very tired and slept) and consequently the other 22 patients received a lower dosage. Twelve patients received a medium dose (clothiapine 15 mg twice daily and [diazepam](#) 10 mg twice daily), and 10 subjects a low dose (clothiapine 5 mg three times daily and [diazepam](#) 5 mg three times a day). The duration of treatment was one week with each drug. The patients were examined prior to the entry in the study and after one and two weeks; they were asked to complete three questionnaires (Inventory Form 1; Symptom Distress Check List; The Tavistock Self Assessment Inventory). Both drugs have a favorable effect on mental symptoms in chronic alcoholics, without statistically significant differences between the two treatments. Patients slightly preferred [diazepam](#) to clothiapine [461].

4.6.V] Delorazepam

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

a) Delorazepam (0.02 milligram/kilogram (mg) intramuscularly (IM)) was more effective than [diazepam](#) (0.14 mg/kg IM) in reducing the psychomimetic adverse effects of [ketamine](#) in 100 patients undergoing elective plastic-reconstructive surgeries and anesthetized with [ketamine](#) (5 to 8 mg/kg IM). No statistical differences were reported for the circulatory adverse effects, and the frequency of emergence phenomena fell from 31% to 14% (p less than 0.05) with delorazepam [520].

4.6.W] Dihydroergotamine

4.6.W.1] Migraine

a) A nonrandomized, nonblinded study of acute treatment of patients with [intractable migraine](#) found superior results were obtained with intravenous [dihydroergotamine](#) plus [metoclopramide](#) every 8 hours compared with intravenous [diazepam](#) every 8 hours [460]. Of 55 dihydroergotamine-treated patients, 49 were headache-free within 48 hours, compared with 7 of 54 diazepam-treated patients. Although the study design is subject to investigator bias, the results suggest that randomized, double-blinded studies are warranted.

4.6.X] Dixyrazine

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

a) Dixyrazine was less effective than [diazepam](#) in preventing anxiety in patients undergoing [cataract surgery](#). In a randomized clinical trial, 100 geriatric patients (age over 70) received either oral dixyrazine

15 to 30 milligrams (mg) or [diazepam](#) 4 to 10 mg as premedication one hour before surgery. Anxiety and sedation were evaluated before and after intervention. Significantly more patients in the dixyrazine group appeared anxious (15 versus 7; p less than 0.05) and needed a supplemental dose of intravenous sedative drugs [485].

4.6.X.2] Depression, Non-agitated

a) Combination dixyrazine (50 milligrams daily) and [imipramine](#) (100 to 200 milligrams daily) was superior to combined [imipramine](#) and placebo and combined [imipramine](#) and [diazepam](#) (10 milligrams daily) in a double-blind, randomized study involving 63 patients diagnosed with non-agitated depression. Clinical efficacy for the dixyrazine-imipramine combination was significantly better (p less than or equal to 0.05) and 86% of the patients in this group were nearly symptom-free at the end of 8 weeks, compared to 67% in both the placebo and [diazepam](#) groups [482]. **PREMEDICATION FOR ENDOSCOPY**

b) Dixyrazine significantly reduced retching in males and regurgitation in both sexes. In a double-blind controlled study, 321 successive patients undergoing [endoscopies](#) were randomized to 1 of 3 premedications: 10 milligrams (mg) of intravenous (IV) dixyrazine plus 0.5 mg of subcutaneous [atropine](#), 5 mg of IV [diazepam](#) plus 0.5 mg of subcutaneous [atropine](#), or [atropine](#) alone. There were no significant differences between dixyrazine and [diazepam](#) in patient's general condition and tenseness before and during the procedure. Dixyrazine significantly reduced retching in men and regurgitation in both men and women (p less than 0.05) and may be considered as a useful alternative premedication for [endoscopy](#) [483].

c) No differences were observed in terms of efficacy between dixyrazine and [diazepam](#) when used as premedication for [gastroscopy](#). In a randomized controlled study, 52 consecutive patients undergoing elective [gastroscopy](#) were randomly assigned to receive intravenously 15 milligrams (mg) of dixyrazine, 7.5 mg of [diazepam](#), or 5 milliliters of saline solution. Both dixyrazine and [diazepam](#) were significantly more effective than placebo in relieving anxiety and eructations (p less than 0.05); however, the difference between the 2 drugs was not significant [484].

4.6.Y] Doxepin

4.6.Y.1] Anxiety

a) No significant difference has been observed in clinical trials in patients with anxiety (with or without depression) between [doxepin](#) and [diazepam](#) [615] [616] [617].

b) A double-blind, placebo-controlled study of 61 outpatients compared [doxepin](#) and [diazepam](#) in the treatment of anxious and anxious-depressive syndromes [618]. After the first week, an enhanced sense of well-being was associated with [diazepam](#). By the end of 6 weeks, there was no significant difference for altering mood and symptomatology with either drug. Objective evaluation rated [diazepam](#) more effective than [doxepin](#) among anxious patients. Drowsiness was the most common side effect. Significant weight gain occurred with [doxepin](#). Possible biases may have been induced by the sampling technique, population characteristics, and consequent drop-out rate.

4.6.Z] Droperidol

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

a) [Droperidol](#) was superior to both [hydroxyzine](#) and [diazepam](#) as a preoperative medication in relief of apprehension or anxiety. This double-blind study in 280 patients reported that 83% who received [droperidol](#) 5 milligrams had no apprehension or anxiety (11% only mildly apprehensive) upon arrival in surgery, as compared with 54% for [hydroxyzine](#) 50 mg, 46% for [diazepam](#) 5 milligrams, and 34% for placebo. There was more drowsiness associated with [droperidol](#) than the other agents, however, fewer [droperidol](#) patients required antiemetics postoperatively [479].

4.6.AA] Fentanyl

4.6.AA.1] Neuropathic pain

a) Patients with neuropathic pain received fentanyl and diazepam (n=27) or fentanyl plus saline (n=26). Of the 27 patients, 14 received fentanyl first and 13 received diazepam first. Patients received a constant rate of medication for a maximum of 5 hours. Fentanyl was administered 5 mcg/kg/hour and diazepam 0.2 mcg/kg/hour. During the observation period (up to 8 hours after the start of infusion) pain, sedation, and side-effects were recorded every 20 minutes. The mean doses of fentanyl and diazepam used were 873 mcg and 52.1 mg, respectively. Fentanyl produced greater maximum and average relief of pain intensity and pain unpleasantness than diazepam or saline. Side effects (episodes/patient) occurred more often in patients who received fentanyl: fentanyl (8.5) vs diazepam (3.58); fentanyl (9) vs (2.54). Severe side effects were not observed in any of the patients [481].

4.6.AB] Flunitrazepam

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

a) Oral flunitrazepam 1 milligram has been comparable with diazepam 10 milligrams as an hypnotic the night before surgery [548]. Oral doses of 1 to 2 mg were at least as effective as oral diazepam 10 to 20 mg, each given 90 minutes prior to surgery, as premedication in a double-blind study involving 142 older children undergoing surgery [550]. In the latter study, flunitrazepam was associated with greater sedation and a tendency toward less vomiting after surgery; amnesic effects were considered greater with flunitrazepam.

b) Sublingual flunitrazepam 2 milligrams was associated with greater sedation than diazepam 10 milligrams orally when each were used as premedication in patients undergoing otorhinolaryngologic surgery. However, the degree of anxiety before the procedure was similar in each group. Adverse effects were also observed to a similar degree with each agent [551].

4.6.AB.2] Premedication for anesthetic procedure

a) The quality of anesthesia was better in patients treated with intravenous (IV) flunitrazepam 1 milligram compared with diazepam 10 milligrams IV as adjuncts to general anesthesia in 90 female patients undergoing abdominal surgery [547]. Each drug was given just prior to surgery. The flunitrazepam-treated patients also required fewer supplementary doses of meperidine and experienced greater amnesic effects.

4.6.AB.3] Efficacy

a) The amnesic effect of flunitrazepam has been greater than that observed with comparable doses of diazepam [548] [547] [549].

4.6.AC] Fluspirilene

4.6.AC.1] Depression

a) Fluspirilene 1 to 1.5 milligrams (mg) weekly for 8 weeks was preferred to diazepam 15 mg daily for its tranquilizing, activating, and antidepressive effects in a cross-over study of 274 patients with depressive and somatic complaints during 3 ongoing trials comparing fluspirilene to placebo and to diazepam. Diazepam and fluspirilene treated somatic complaints equally well; however, the diazepam group reported increased initial hypnotic effects. Twelve out of 225 patients received treatment for akathisia due to a cumulative effect after 5 weeks of treatment with fluspirilene. In everyday practice, fluspirilene may be preferable over diazepam for its once-weekly administration at the doctor's office and for its nonaddictive properties.

Fluspirilene may also be superior to [diazepam](#) in patients requiring a tranquilizer with activating and anti-depressive effects [486].

4.6.AD] Gepirone

4.6.AD.1] Anxiety

a) SUMMARY: Gepirone is less effective than [diazepam](#).

b) Gepirone was less effective than [diazepam](#) in [generalized anxiety disorder](#) in a double-blind study [487]. With gepirone in average doses of 20 milligrams (mg) daily, onset was slow, with superiority over placebo not being achieved until week 6, and a high incidence of adverse effects was observed; each of these factors contributed a high attrition rate (58% by week 8). In contrast, [diazepam](#) in the same dose produced significant clinical benefit within one week, which was sustained; attrition rates were lower than with gepirone, and improvements in HAM-A scores were consistently better. The predominant adverse effect of [diazepam](#) (sedation) was considered beneficial by patients, whereas gepirone adverse effects were not (eg, dizziness, nausea, insomnia).

4.6.AE] Halazepam

4.6.AE.1] Anxiety

a) Limited data indicates that [halazepam](#) is at least as effective as [diazepam](#) when administered in comparable doses. Available data, however, are conflicting, and there have been only limited comparative evaluations between the 2 drugs. These studies must be evaluated in relation to equipotent doses since 1 study demonstrated [diazepam](#) less effective than [halazepam](#) using only 20 mg/day of [diazepam](#) [676]. However, [diazepam](#) was slightly more effective than [halazepam](#) in a 6-week, double-blind, placebo-controlled study with 62 patients and 68 controls [677]. [Halazepam](#) does not have any advantage over [diazepam](#) for any condition. Further controlled studies are required to assess the subtle differences between the two drugs.

4.6.AE.2] Adverse Effects

a) [Halazepam](#) was evaluated to have a lower abuse potential than [diazepam](#) in patients treated for alcoholism. Thirty alcoholics were administered [halazepam](#) 160 or 320 mg, [diazepam](#) 20 or 40 mg, and placebo in a triple crossover, double-blind fashion. The euphoric feeling induced by the benzodiazepines were subjectively evaluated by each subject. [Halazepam](#) took longer to induce the drunk-like feeling than [diazepam](#) and the higher dose of this agent did not intensify the euphoric feeling, as noted with [diazepam](#) [678].

4.6.AF] Haloperidol

4.6.AF.1] Schizophrenia

a) [Haloperidol](#) was compared with placebo, [chlorpromazine](#), [diazepam](#), and [imipramine](#) as prophylactic agents to prevent [relapse](#) of schizophrenic patients. At the end of the three year trial, [haloperidol](#) and [chlorpromazine](#) significantly prolonged remission as compared to the other three treatments. Daily doses of [haloperidol](#) were 3 mg; [chlorpromazine](#) doses were 75 mg [513].

4.6.AG] Imipramine

4.6.AG.1] Depression

a) An 8-week, double-blind, controlled study compared the efficacy of [alprazolam](#) (58 patients), [diazepam](#) (59 patients), [imipramine](#) (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III

diagnosis of [major depression](#). Week 1 was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assigned medication, and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remaining 4 days. At the end of the study the mean daily doses were 143 mg [imipramine](#), 3.1 mg [alprazolam](#), 24 mg [diazepam](#), and 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion of the study, 41% of the [imipramine](#) group had withdrawn, 23% of the [alprazolam](#) group, 44% of the [diazepam](#) group, and 40% of the placebo group. The main reason given for attrition was side effects with the active compounds and ineffectiveness with placebo. [Alprazolam](#) and [imipramine](#) were both significantly better than placebo in treating depression, but [diazepam](#) was not effective. The clinical effects of [imipramine](#) and [alprazolam](#) were equivalent, and overall the frequency of side effects was similar. [Imipramine](#) produced less drowsiness and more anticholinergic effects than both [alprazolam](#) and [diazepam](#) [555].

4.6.AH] Ipsapirone

4.6.AH.1] Anxiety

a) Ipsapirone 15 to 30 milligrams daily is similar in efficacy to [diazepam](#) 15 milligrams daily in the treatment of [generalized anxiety disorder](#) [518] [519]. However, anxiolytic effects occur faster with [diazepam](#); in one study, [diazepam](#) was clearly superior to ipsapirone after one week of treatment, although both agents were similarly effective after 4 weeks [518].

b) [Diazepam](#) also appears to be better tolerated than ipsapirone. In one placebo-controlled comparative study (n=249) [519], termination of therapy due to adverse effects was reported in 29% and 42% of anxiety patients treated with ipsapirone 15 milligrams daily and 30 mg daily, respectively, compared with 8% of those receiving [diazepam](#) 15 milligrams daily. The most frequent adverse effects necessitating withdrawal of therapy were sedation with [diazepam](#) and nausea or dizziness/lightheadedness with ipsapirone. Gastrointestinal adverse effects were also greater with ipsapirone compared to [diazepam](#) in a further study [518], although other adverse effects (including sedation) occurred with similar frequency.

4.6.AI] Ketazolam

4.6.AI.1] Anxiety

a) SUMMARY: Several controlled trials have reported that once daily ketazolam is at least as effective as [diazepam](#) given 3 times daily in the treatment of anxiety [524] [523] [525] [522] [526] [521]. In some reports, the superiority of ketazolam has been suggested [521] [526]; however, differences observed in these studies are of doubtful clinical significance. In most studies, oral ketazolam 30 to 60 milligrams once daily has been as effective as [diazepam](#) 5 to 10 milligrams orally 3 times daily (15 to 30 mg daily), indicating that ketazolam is approximately half as potent as [diazepam](#) on a milligram basis. The onset of action with both agents has been similar, with significant reductions in anxiety occurring after 1 to 2 weeks of therapy.

b) Once daily ketazolam may, however, not always be comparable to multiple daily [diazepam](#) doses. Sixty-nine percent of anxiety patients were controlled on single daily doses of ketazolam. However, 31% of patients required a twice daily regimen to achieve results similar to those obtained with [diazepam](#) 3 times daily. Thus, once daily ketazolam may not be optimal for all patients [525].

4.6.AI.2] Spasticity

a) SUMMARY: Two small controlled studies have reported the similar efficacy of ketazolam and [diazepam](#) in the treatment of spasticity due to [multiple sclerosis](#) or [stroke](#) [527] [528].

b) Ketazolam 10 to 20 milligrams orally 3 times daily was as effective as [diazepam](#) 5 to 10 milligrams orally 3 times a day in relieving spasticity in a double-blind, crossover study involving 39 patients with [multiple sclerosis](#) or [stroke](#) [528]. Both agents were superior to placebo. The primary adverse effects observed with

both ketazolam and diazepam were drowsiness, tiredness, and weakness; these occurred in 30% of patients in each group.

c) Ketazolam and diazepam were compared in 14 severely spastic inpatients with chronic multiple sclerosis in a 42-day, double-blind, crossover study [527]. Ketazolam was given as 30 milligrams/day in the evening during the first week, with doses being doubled in the second week. Diazepam 5 milligrams orally 3 times daily was administered during week 1, with the dose being doubled to 10 mg 3 times a day in the second week. Ketazolam was more effective than placebo in relieving spasticity in 7 of the 14 comparisons, whereas diazepam was superior to placebo in 6. Comparisons of diazepam with ketazolam revealed that ketazolam was superior to diazepam in 7 comparisons, equal to diazepam in 5, and less effective than diazepam in 2. Adverse effects were slightly less with ketazolam as compared with diazepam. Drowsiness occurred in 8 diazepam patients and 3 ketazolam patients, as compared with 4 placebo patients; lightheadedness was observed in 4, 5, and 0 patients, respectively.

4.6.AI.3) Adverse Effects

a) In some studies the incidence of sedation or drowsiness has been less with ketazolam as compared to diazepam [521] [522]. However, other studies have not demonstrated this advantage of ketazolam [523] [524]. In the largest comparative study to date, involving 783 evaluable patients, drowsiness was observed in 31% and 40% of patients receiving ketazolam and diazepam, respectively; drowsiness was observed in 18% of placebo patients [522]. Although the lower incidence of drowsiness with ketazolam was statistically significant due to the large sample size, the similarity of these percentages raise doubt as to the actual clinical significance of the finding.

4.6.AJ] Lorazepam

4.6.AJ.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 [646]. 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.AJ.2] Anxiety

a) In the treatment of anxiety, most studies indicate that both diazepam and lorazepam are equally [636] [637] [638] [639] [640]. Marginal differences in terms of efficacy on specific parameters (Hamilton Rating Scale) and side effects have been reported, but do not appear to be statistically significant [636] [638]. Lorazepam is more likely to impair memory recall in patients undergoing surgery when used as an intravenous premedication [641]. 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 [642]. 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 [637] [643] [644]. A double-blind study was conducted involving 73 patients suffering from uncomplicated anxiety states as defined by the Glossary of Mental Disorders [643]. 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** [645].

4.6.AJ.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) [647].

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) [648]. 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 [649]. 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 [650]. Both drugs were reported to be similarly effective in controlling seizures. The mean dose of **diazepam** required to control seizure activity was 0.38 +/- 0.21 milligram/kilogram (range, 0.09 to 0.71 mg/kg). The mean dose of **lorazepam** required for seizure control was 0.11 +/- 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.AK] **Lormetazepam**

4.6.AK.1] **Administration of medication - Preoperative care**

a) In a study comparing lormetazepam and **diazepam** for premedication, lormetazepam 2 milligrams demonstrated equal efficacy to **diazepam** 15 milligrams when given 1.5 to 3 hours prior to surgery. An equivalent number of patients were sedated and both drugs exhibited anxiolytic efficacy. There was a trend towards a greater anxiolytic effect with lormetazepam. However, standard scoring systems could not exhibit a statistically significant difference between the agents. A lesser extent of dizziness was noted with lormetazepam [535]. A third study utilizing sublingual lormetazepam 2.5 milligrams or intravenous

[diazepam](#) 10 milligrams as premedication for extraction of impacted third molars. Surgeons rated the agents as having equal efficacy while patient preference was for [diazepam](#) [536].

4.6.AK.2] Anxiety

a) Lormetazepam demonstrated equal efficacy to [diazepam](#) and superiority over placebo for the treatment of anxiety. Ten psychiatric patients were randomized to receive either lormetazepam 1 milligram oral drops or [diazepam](#) 2 milligrams twice daily for 4 weeks after one week of placebo. In this study, [lorazepam](#) demonstrated an anxiolytic effect similar to [diazepam](#) and exhibited few side effects. Both drugs were well-tolerated for the 40 days of the study [532].

4.6.AK.3] Insomnia

a) Lormetazepam 1 milligram was compared to [diazepam](#) 5 milligrams for insomnia and lormetazepam was proven to be superior. One hundred patients were randomized to receive either lormetazepam or [diazepam](#) for 7 days. Lormetazepam demonstrated significantly better results than [diazepam](#) for reduction of time to fall asleep, prolongation of uninterrupted sleep and reduction in frequency of awakening. Lormetazepam also displayed no hangover effects and had a lesser number of side effects [533] [534].

4.6.AL] Loxapine

4.6.AL.1] Anxiety

a) [Diazepam](#) was superior to [loxapine](#) in the treatment of anxiety. [Diazepam](#) 17.5 milligrams every day (average dose) was compared with [loxapine](#) 9.6 milligrams every day (average dose) in 57 adults suffering from severe anxiety. The Hamilton Psychiatric Rating Scale for Anxiety, Nurses Observation Scale, and Lipman Self-Rating Symptom Scale were used to measure treatment efficacy. One patient developed mild ataxia on [loxapine](#) therapy; 2 patients developed drowsiness and 1 developed muscle atony on [diazepam](#) therapy [635].

4.6.AM] Magnesium

4.6.AM.1] Eclampsia

a) Magnesium sulfate is superior to [diazepam](#) for the treatment of [eclampsia](#), according to a Cochrane Review, which included 7 trials involving 1441 women with [eclampsia](#). In comparison to the risk with [diazepam](#), the relative risk (RR) of maternal death with magnesium was 0.59 (95% confidence interval (CI) 0.37 to 0.94). The risk of recurrence of convulsions was also lower with magnesium than with [diazepam](#): RR=0.44, 95% CI 0.34 to 0.57. With magnesium, there were fewer babies with Apgar scores below 7 at 5 minutes (RR=0.72, 95% CI 0.55 to 0.94) and fewer babies with a hospital stay exceeding 7 days (RR=0.66, 95% CI 0.46 to 0.95) [537].

b) A randomized trial involving 51 women was conducted to compare the effectiveness of [diazepam](#) to magnesium sulfate in the treatment of convulsions due to [eclampsia](#) [538]. Magnesium sulfate (n=27) was administered as an intravenous bolus of 4 grams over 3 to 5 minutes followed by an [intramuscular injection](#) of 10 grams; if convulsions reoccurred an additional 2 grams magnesium sulfate was given intravenously followed by 5 grams intramuscularly every 4 hours for up to 24 hours. [Diazepam](#) (n=24) was given in a dose of 10 milligrams intravenous bolus and repeated if the convulsions occurred again; this was followed by a [continuous intravenous infusion](#) of [diazepam](#) for up to 48 hours. A significantly lower number of neonates in the magnesium group experienced low Apgar scores. There was no significant difference in maternal outcomes between the 2 groups. In the magnesium group there were 2 early neonatal deaths and in the [diazepam](#) group there were 3 stillbirths. Three women in the [diazepam](#) group developed [pneumonia](#); none in the magnesium group developed [pneumonia](#). [Cardiac arrest](#) occurred in 1 patient in the magnesium

group, possibly due to rapid administration of magnesium. A large proportion of the study population (67%) received [diazepam](#) prior to randomization. Maternal morbidity was higher for both treatment groups if [diazepam](#) was given prior to randomization, but it was less if the patient received magnesium after randomization. Larger scale studies are needed to determine if magnesium has a clinically significant advantage over [diazepam](#) in treating convulsions due to [eclampsia](#).

4.6.AN] Medazepam

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

a) A single oral dose of medazepam 10 milligrams provided less sedation than [diazepam](#) 10 milligrams orally and was comparable to that encountered with placebo. Medazepam or [diazepam](#) did not significantly reduce apprehension compared to placebo. Emetic episodes were more frequent in those patients receiving medazepam compared to [diazepam](#). Assessments of effects were conducted at 20, 40, 60, and 90 minutes following administration of the investigational agent in 150 women undergoing minor [gynecological surgeries](#) of similar duration. All women received the same anesthetic [539]. The specific standardized tool used for assessing drowsiness, anxiety, and side effects was not stated.

4.6.AO] Melperone

4.6.AO.1] Anxiety

a) As an anxiolytic, oral melperone was as effective as oral [diazepam](#) in a study in elderly patients having [cataract surgery](#) under [regional anesthesia](#), but hypotension was seen in 5 melperone-treated patients with vascular disorders [540]. Melperone 15 to 30 milligrams (n=50) and [diazepam](#) 4 to 10 milligrams (n=50) were given 1 hour preceding surgery. Blinded, subjective assessments of the patients' mood revealed no significant differences in anxiety between the 2 groups. Five melperone-treated patients and 1 diazepam-treated patient experienced hypotension (a 40% decrease in systolic blood pressure from preoperative measure); 4 of these patients had bradycardia. Five of these 6 patients had taken their usual dose of antihypertensive and/or antianginal medication the day of surgery.

b) The effects of melperone, [chlorpromazine](#), [haloperidol](#), and [diazepam](#) on artificially-induced anxiety were compared in normal subjects [541]. Autonomic (skin conductance) response evoked during aversive classical conditioning was measured in eleven healthy subjects. Single oral doses of placebo, melperone 10 milligrams, melperone 50 milligrams, [chlorpromazine](#) 50 mg, [diazepam](#) 10 milligrams, and [haloperidol](#) were administered randomly to each member of the study group. There was a minimum of 10 days between tests. Judging from the data which indicates a subject's anxiety level in this experimental setting (skin conductance level during habituation and reinforcement, its pattern of changes and fluctuations, etc), it may be concluded that [diazepam](#), melperone 50 milligrams, and [chlorpromazine](#) are effective anxiolytics. Whereas melperone 50 milligrams reduced skin conductance level and eliminated anticipatory responses, melperone 10 milligrams (as well as [haloperidol](#)) had no effect upon conditioned and unconditioned responses.

4.6.AP] Meperidine

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

a) [Diazepam](#) lowers both anxiety and the metabolic rate better than [meperidine](#). Three groups of 14 healthy patients scheduled for hand surgery were compared for response to premedications which included either 50 milligrams intramuscular [meperidine](#) plus 0.5 mg [atropine](#), 10 milligrams oral [diazepam](#) plus placebo (saline) injection, or placebo tablet plus saline injection. Clinical response was assessed by patients with a visual analog scale rating tiredness, anxiety, fear, and dry mouth. Metabolic response was determined by continuous (30 minute) [measurement of oxygen consumption](#) and calculation of energy

expenditure. Anxiety scores were lowest for [diazepam](#). Oxygen consumption was higher than the calculated basal metabolic rate (BMR) in all groups for the first 10 minutes after medication. The [diazepam](#) group stabilized much earlier than the others and had lower energy consumption throughout [667].

4.6.AQ] [Meprobamate](#)

4.6.AQ.1] Anxiety

a) [Diazepam](#) 5 to 10 milligrams three times/day was more effective in reducing anxiety than [meprobamate](#) 400 to 800 milligrams three times/day in a double-blind, cross-over study of 5 adult patients [531].

4.6.AR] [Metaclozepam](#)

4.6.AR.1] Anxiety

a) [Metaclozepam](#) 15 milligrams (mg) per day was slightly more effective than [diazepam](#) 15 mg/day in the treatment of 131 outpatients with neurotic anxiety syndrome in a four-week, double-blind study. Anxiolytic efficacy was assessed using the Clinical Global Impressions (CGI) and the Hamilton Anxiety Scale (HAMA) (physician's rating) as well as the Erlangen Anxiety Scale (EKSA), the Scale of Well-being and the List of Complaints by Zerssen (patient's rating). Both benzodiazepines produced a significant improvement in the severity of the disease (84.1% of the patients in the [metaclozepam](#) group and 80.7% of the patients in the [diazepam](#) group). However, [metaclozepam](#) demonstrated statistically significant superiority over [diazepam](#) in the CGI items 'severity of illness' and 'somatic anxiety' and was slightly inferior in two HAMA subscales ('psychic anxiety' and 'somatic anxiety'). In addition, fewer adverse effects were reported with [metaclozepam](#) therapy (tiredness and vertigo being most common - 29 of 69 [metaclozepam](#) versus 49 of 62 [diazepam](#) patients) [544] [545].

b) In a double-blind study of 50 outpatients with anxious-depressive disorders, no difference in efficacy was found between [metaclozepam](#) and [diazepam](#) therapy. Patients were treated with oral doses of either 20 milligrams (mg) of [metaclozepam](#) or 16 mg of [diazepam](#) per day for four weeks. Both groups showed a significant decrease of anxiety scores in the Hamilton Anxiety Scale (HAMA) as well as in the Anxiety Scale of Zung (SAS) after the first week of therapy. However, daytime fatigue and dizziness were caused in 16 patients (67%) of the [diazepam](#) group and 3 patients (12%) of the [metaclozepam](#) group. Twenty-two patients of the [metaclozepam](#) group (88%) and 16 patients of the [diazepam](#) group (67%) did not require medication after the end of the study [546].

4.6.AS] [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 [552]. 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.AT] [Methocarbamol](#)

4.6.AT.1] Musculoskeletal pain

a) **Diazepam** 2 milligrams orally four times/day was equivalent to **methocarbamol** 1 gram orally four times day in the relief of muscle spasm and improvement in range of motion for 37 patients [542]. This double-blind, randomized, crossover trial treated 59 patients for 3 days to 2 weeks with either active drug or placebo. It was not stated whether additional analgesic or muscle relaxant medications and physical therapy were allowed. Among 37 crossover patients, the two drugs were demonstrated equivalent in the relief of pain and muscle spasm; however, **diazepam** was more effective in relieving anxiety and improving daily activity. A clear advantage for **diazepam** over **methocarbamol** could not be demonstrated based on the inappropriate use of a statistical test on the symptom scores [543].

4.6.AU] Midazolam**4.6.AU.1] Administration of medication - Preoperative care**

a) Most studies have reported the comparable efficacy of **midazolam** and **diazepam** in producing sedation prior to local **anesthesia** for short operative procedures such as **gastroscopy**, **endoscopy**, **cardiac catheterization**, dentistry, and in conjunction with **spinal anesthesia** (Wright et al, 1993) [567] [568] [569] [570] [571] [572] [573] [574] [575] [576]. In some studies, **midazolam** had a faster onset of effect and greater degree of early sedation than **diazepam** [568] [575] [569]; (Wright, 1993), whereas others have reported a similar onset of action [577] [578]. In all studies, the degree of amnesia produced by **midazolam** was greater than that of **diazepam**, and a lower order of venous complications and **phlebitis** occurred in midazolam-treated patients. However, one study reported a higher incidence of respiratory side effects such as hiccoughs, brief **apnea**, and **airway obstruction** with **midazolam** [579]. **Midazolam** may also produce slightly greater hypoxemia [580]. Recovery times have varied, with some reports suggesting a slower recovery following **midazolam** as compared with **diazepam** [578] [568], and others reporting a slower recovery with **diazepam** (Wright et al, 1993) [581]; (Barker et al, 1986) or increased sedation later in the day with **diazepam** [582]. However, in most studies recovery times were similar. **Midazolam** is three to four times as potent per milligram as **diazepam** [583]. A dose ratio of 4 to 5:1 (**diazepam:midazolam**) produced comparable sedation in a cross-over study on 11 healthy subjects [581].

b) **Diazepam** 0.25 mg/kg was no more effective than **alprazolam** 0.005 mg/kg, **midazolam** 0.3 mg/kg, or placebo as an oral premedication in children 4 years or older and up to 50 kg in a double-blind, placebo-controlled study [584]. All children underwent day surgery. There was no significant difference among any of the medications or placebo in anxiolytic effects. Time to awaken was significantly longer with **diazepam** than with placebo (30 vs 22 min), but there was difference in time to awaken with either **alprazolam** or **midazolam**.

4.6.AU.2] Induction of general anesthesia

a) **Midazolam** 0.15 mg/kg IV produced a shorter induction time, less **apnea**, and reduced venous irritation as compared with **diazepam** 0.25 mg/kg IV for **induction of anesthesia** in seriously ill, high-risk patients [566].

4.6.AU.3] Sedation

a) In a randomized, double-blind study, **midazolam** and emulsified **diazepam** produced a similar quality of conscious sedation (p greater than 0.05) during **endoscopic procedures** [585]. Dosed for adequate sedation, patients received either **midazolam** (n=100) (mean dose 10.5 milligrams (mg)) or emulsified **diazepam** (n=111) (mean dose 3.8 mg). There was no difference in time to adequate sedation, recovery time, requirement for reversal agents, oxygen supplementation required, or **phlebitis** (all p greater than 0.05).

b) Intravenous (IV) [midazolam](#) 0.07 milligram/kilogram (mg/kg) was similar to IV [diazepam](#) 0.15 mg/kg in providing sedation and enhancing cooperation during [upper gastrointestinal endoscopy](#) in a double-blind study involving 23 patients. The speed of recovery from sedation was also similar between agents, as were the effects on arterial blood pressure and heart rate. However, amnesia was greater with [midazolam](#) when compared to [diazepam](#), and patient acceptability for the procedure was higher in the [midazolam](#) group. [Midazolam](#) is considered the agent of choice when amnesia is desirable, such as in repeated [endoscopies](#) [567].

c) Intravenous (IV) [midazolam](#) 0.07 milligram/kilogram (mg/kg) offered no clinical advantage over IV [diazepam](#) 0.15 mg/kg as premedication for [endoscopy](#). In addition, [midazolam](#) carries an increased risk of oversedation when dosed on a milligram-per-kilogram basis [586].

d) Mean [midazolam](#) doses of 11.3 milligrams (mg) for men and 10.7 mg for women resulted in significantly more retching in 100 patients undergoing [endoscopy](#) than did intravenous [diazepam](#) (Diazemuls) 10 mg plus intravenous pethidine, 50 to 75 mg [587].

4.6.AU.4] Seizure

a) IM [midazolam](#), compared with IV [diazepam](#), significantly shortened time to medication administration (7.8 vs 3.3 minutes) but not time from drug administration to seizure cessation (mean, 5 minutes) in children (N=24) with motor seizures of at least 10 minutes duration. IM [midazolam](#) dosage was 0.2 mg/kg to a maximum of 7 mg, and IV [diazepam](#) dosage was 0.3 mg/kg to a maximum of 10 mg [588].

b) Buccal [midazolam](#), compared with rectal [diazepam](#), significantly shortened time to seizure cessation after administration in adults with [convulsive status epilepticus](#) (2.8 vs 5 minutes) but not in patients with non-convulsive [status epilepticus](#) or convulsive or non-convulsive serial seizures (7.6 vs 7.4 minutes). Cessation of seizures within 10 minutes of administration was not significantly different (74.4% vs 83.3%) in 80 episodes in 22 adults in a residential facility; all caregivers, and 6 of 7 patients who received both treatments, preferred buccal [midazolam](#) [589].

c) Buccal [midazolam](#) (10 mg/2 mL), compared with rectal [diazepam](#) (10 mg), produced a nonsignificant difference in seizure cessation within 10 minutes (75% vs 59%) in a randomized study (79 seizure episodes) at a residential center for children with seizure disorders (N=28) [590].

d) A single dose of intranasal [midazolam](#), compared with rectal [diazepam](#), produced nonsignificant differences in suppression of clinical seizure activity within 15 minutes (82% vs 89%) and time to seizure cessation (4.6 vs 4.3 minutes) in 124 exacerbations in a crossover trial (N=21) of adults with [epilepsy](#) in a residential treatment facility; 16 of 21 patients and their caregivers preferred intranasal [midazolam](#) [591].

e) Intranasal [midazolam](#), as home treatment for seizures lasting longer than 5 minutes, produced a total seizure time after administration that was not significantly different compared with rectal [diazepam](#) (3 vs 4.3 minutes) in a randomized trial (N=92). [Midazolam](#) 0.2 mg/kg was administered with the Mucosal Atomization Device [592].

f) Intranasal [midazolam](#), compared with rectal [diazepam](#), stopped significantly more seizures within 10 minutes of administration (87% vs 60%) in a randomized pediatric study (N=45). Intranasal [midazolam](#) 0.2 mg/kg or rectal [diazepam](#) 0.3 mg/kg was administered in the emergency department for any type of seizure, mainly generalized tonic-clonic. In the [midazolam](#) group, one patient had tachypnea at 5 minutes and another had [tachycardia](#) at 10 minutes [593].

g) Intranasal [midazolam](#), compared with IV [diazepam](#), significantly shortened the average time from hospital arrival to treatment initiation (3.37 vs 14.13 minutes) and from hospital arrival to seizure cessation (6.67 minutes vs 17.18 minutes) but did not significantly affect average time from drug administration to seizure control (3.01 vs 2.67 minutes) in a randomized trial (N=50) of patients 1 month to 12 years old with acute motor seizures lasting at least 10 minutes [594].

h) There was no significant difference between intranasal [midazolam](#) and IV [diazepam](#) in the cessation of seizure activity within 5 minutes (88% vs 92%), but [midazolam](#) significantly shortened mean time from hospital arrival to seizure cessation (6.1 versus 8 minutes) in children with [febrile seizures](#) lasting at least

10 minutes (N=44; age range, 6 months to 5 years). Intranasal [midazolam](#) dosage was 0.2 mg/kg, and IV [diazepam](#) dosage was 0.3 mg/kg up to 10 mg [595].

4.6.AU.5] [Status epilepticus](#), Refractory

a) In a randomized study (N=40) of children with refractory [status epilepticus](#) (seizures uncontrolled after 2 IV [diazepam](#) doses and [phenytoin](#) infusion), IV infusions of [midazolam](#), compared with [diazepam](#), produced a nonsignificant difference in seizure control (86% vs 90%) and mean time to attainment of control (about 16 minutes for both treatments), but a significantly higher rate of seizure recurrence (57% vs 16%) and mortality (8 vs 2 patients). [Midazolam](#) was administered as a 0.2 mg/kg-bolus followed by a continuous IV infusion starting at 2 mcg/kg/min and increasing at 5-minute intervals until seizures were controlled or the maximum of 10 mcg/kg/min was reached; [diazepam](#) was administered as a continuous IV infusion of 0.01 mg/kg/min, increasing every 5 minutes by 0.01 mg/kg/min until seizure control or to a maximum of 0.1 mg/kg/min. Infusions continued for at least 6 hours after control was achieved and then were gradually tapered over 12 to 24 hours. If seizures recurred after initial control, the infusion rate was increased. If seizures were not controlled with the study drug, patients were given [thiopental](#) [596].

4.6.AV] [Mirtazapine](#)

4.6.AV.1] [Anxiety about treatment - Insomnia](#), Preoperative

a) [Mirtazapine](#) 15 milligrams and [diazepam](#) 10 milligrams were similarly effective in reducing insomnia and anxiety when given the night prior to [gynecological surgery](#) in a placebo-controlled study (n=250). Each agent was superior to placebo in enhancing and improving sleep and sleep quality the night before and alleviating presurgical anxiety the following morning. Trends toward less nighttime awakening, longer sleep, and greater morning sleepiness were seen with [mirtazapine](#), although these differences were not significant [558].

4.6.AW] [Morphine](#)

4.6.AW.1] [Pain](#)

a) [Morphine](#) 10 milligrams (mg) intramuscularly (IM) was generally more effective than [diazepam](#) 10 milligrams (mg) IM for the management of postoperative pain, as was expected in a randomized, double-blind study [668]. [Diazepam](#), however, did produce significant analgesia (equivalent to [morphine](#)) 30 minutes after administration. Administration of 5 mg of [morphine](#) with 5 mg of [diazepam](#) produced the equivalent analgesic effect as 10 mg [morphine](#) without the high incidence of nausea associated with the use of [morphine](#) alone. The authors' statement "---in the doses used, [morphine](#) alone was superior to the morphine-diazepam combination as far as intensity of analgesia is concerned" is not supported by their data because the mean pain scores of both groups are almost identical and no statistical information was provided to prove a significant difference.

4.6.AX] [Nabilone](#)

4.6.AX.1] [Anxiety](#)

a) The antianxiety effect of [nabilone](#) (2 milligrams (mg)) and [diazepam](#) (5 mg) in a single-dose double-masked study. Anxiety induced by an experimental procedure was more effectively alleviated by [diazepam](#) than by [nabilone](#) [634].

4.6.AY] [Opipramol](#)

4.6.AY.1] Anxiety

a) A randomized double-blind, placebo-controlled trial found [diazepam](#) to be more efficacious and cause fewer adverse effects than dixyrazine, opipramol and placebo when treating patients with anxiety-tension states. There were 23 patients in the opipramol, dixyrazine and placebo groups and 26 in the [diazepam](#) group. The medication was administered three times daily with total daily doses as follows: 150 to 200 milligrams (mg) of opipramol, 30 to 40 mg of dixyrazine and 12 to 16 mg of [diazepam](#). An anxiety rating scale which reviewed symptoms, signs and social functioning capacity was used along with adverse effects and global effects (both subjective and objective) to evaluate therapeutic outcome. The [diazepam](#) group obtained the best outcome; however, only 50% of patients demonstrated a definite improvement as measured by the global effects. Results in all other areas were also found to be better with [diazepam](#), dixyrazine was next and opipramol had results only slightly better than the placebo group. The antidepressive effect of opipramol was demonstrated to be very low in this study. The adverse effects in all groups were very mild, dry mouth was more common in the opipramol group and weight gain in the dixyrazine group (Arfwidsson, 1971).

4.6.AZ] Opium**4.6.AZ.1] Drug withdrawal seizure - Opioid withdrawal**

a) SUMMARY: Opium can control neonatal narcotic withdrawal seizures better than [diazepam](#) but it entails a longer period of treatment compared to [phenobarbital](#) [556] [557].

b) Camphorated tincture of opium (Paregoric(R)) was more effective than [diazepam](#) in controlling [neonatal seizures](#) secondary to narcotic withdrawal [557]. At a dose of 0.2 to 0.8 milliliter every 3 hours, Paregoric(R) produced adequate clinical response in 6 (86%) of 7 neonates with narcotic withdrawal seizures. None of a similar group of 10 neonates had good seizure control with [diazepam](#) given at doses of 0.5 to 2.5 milligrams intramuscularly every 8 hours.

4.6.BA] Oxazepam**4.6.BA.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 milligrams, [diazepam](#) 10 mg, [lorazepam](#) 2 mg, or [oxazepam](#) 30 milligrams. [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 [675].

4.6.BA.2] Adverse Effects

a) [Oxazepam](#) has demonstrated less of an abuse potential than [diazepam](#). Twelve subjects with a history of hypnotic drug abuse were administered single doses of [diazepam](#) (10 to 160 milligrams), [oxazepam](#) (30 to 480 milligrams), and placebo for 3 days in a double-blind, crossover fashion. [Diazepam](#) produced barbiturate-like effects more frequently than [oxazepam](#) and was preferred for this euphoric affect. Tolerance to psychomotor and cognitive effects developed to [oxazepam](#) and not to [diazepam](#). [Oxazepam](#) was also identified as a placebo significantly more often than [diazepam](#) [674].

4.6.BB] Phenobarbital**4.6.BB.1] Delirium tremens**

a) In a retrospective study (n=194), [diazepam](#) did not differ from [phenobarbital](#) in length of hospital stay or duration of [delirium tremen](#) among alcoholic patients. Study subjects had a history of alcoholism, heavy alcohol intake within the past 96 hours, two physical alcohol withdrawal symptoms (tremor, sweat, or psychomotor agitation), visual hallucinations, and a turbid and disoriented state. Patients came from 3 different study sites. Patients from two centers received hourly oral or IV [phenobarbital](#) 100 to 200 mg (n=106) while cohorts from another center received IV [diazepam](#) 10 to 20 mg every hour (n=88; adjusted to 2 to 3 times/hr dosing schedule if no response) until the onset of sleep. The mean blood alcohol concentration before intervention was approximately 0.9 g/L in the [phenobarbital](#) group compared with 1.53 g/L in the [diazepam](#) group (p=0.049), and relatively fewer patients treated with [phenobarbital](#) compared with [diazepam](#) had prior DT (27% vs 38%). The analysis revealed no significant difference between [phenobarbital](#) and [diazepam](#) in the efficacy endpoints of mean length of hospital stay (12.2 to 13 days vs 12.3 days) and mean DT duration (5.3 to 5.85 days vs 6.64 days) between treatment arms. Eight patients (9%) did not respond to [diazepam](#) (ie, sleep was not achieved) despite large [diazepam](#) doses equivalent to 1274 mg, and subsequently responded successfully to [phenobarbital](#). [Phenobarbital](#) and [diazepam](#), respectively, was associated with respiratory complications (37% vs 43%), cardiovascular complications (13% vs 10%), [pneumonia](#) (25% vs 27%), [respiratory depression](#) (3.8% vs 1%), and fatal outcomes (3% vs 1%). Three of the deaths were related to complications from respiratory and cardiovascular insufficiency [665].

4.6.BB.2] 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). 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) [663].

b) An intravenous (IV) regimen of [phenobarbital](#) (with the addition of [phenytoin](#) if required) was reported as effective as the combination of [diazepam](#) and [phenytoin](#) IV in the treatment of [status epilepticus](#) in a randomized, non-blinded study. In 1 group, [diazepam](#) was given initially in doses of 2 milligrams/minute IV, with the infusion being terminated when the patient stopped seizing or after 20 mg total was administered. [Phenytoin](#) was given concurrently at a rate of 40 milligrams/minute; loading doses of 18 mg/kg were given if serum levels were unknown or between 0 and 4 mg/L. In another group [phenobarbital](#) was given at a rate of 100 mg/minute until doses of 10 mg/kg were administered; a [phenytoin](#) infusion was initiated concurrently if patients continued to seize 10 minutes after initiation of [phenobarbital](#) therapy. Cumulative convulsion time was shorter in phenobarbital-treated patients (5 versus 9 minutes), as was response latency (5.5 versus 15 minutes). Complications occurred to a similar degree in each group, including [arrhythmias](#) and hypotension. These data suggest that the [phenobarbital](#) regimen is at least as effective and safe as the conventional [diazepam/phenytoin](#) regimen. Monotherapy with [phenobarbital](#) was effective in 11 of 18 patients treated in this series [664].

4.6.BC] Phenytoin

4.6.BC.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) [679]. 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.BD] Pinazepam

4.6.BD.1] Anxiety

a) Limited studies have suggested that pinazepam is at least as effective as **diazepam** in anxiety disorders [560]. However, studies were small and poorly designed. A well-controlled study is needed to assess comparative efficacy.

b) In one outpatient study, mean effective doses of **diazepam** and pinazepam were comparable (22.5 mg daily and 20 mg daily, respectively) [560].

4.6.BE] Prazepam

4.6.BE.1] Anxiety

a) SUMMARY: Studies indicate that **prazepam** is as effective as **diazepam** and **clorazepate** in treating anxiety and more effective than placebo [514].

b) **Prazepam** 30 milligrams in divided doses three times a day or as a single dose at night was compared with **diazepam** 15 mg (in divided doses TID or at night) in the treatment of anxiety in a single blind study involving 2009 patients [515]. Utilizing the Hamilton Anxiety Rating Scale scores and Physicians' Global Assessment of response, patients treated with **diazepam** reportedly did not respond as well as prazepam-treated patients, and had a greater return of anxiety symptoms after withdrawal of treatment. Side effects were reported to be less severe in prazepam-treated patients, particularly with divided daily **dose regimens**. Dizziness was reported to be least apparent with **prazepam** in single bedtime doses. However, none of these findings were statistically significant and although the authors recommend that **prazepam** is preferable to **diazepam** for the treatment of anxiety, the study did not prove a definite statistical advantage even with the large number of patients employed.

4.6.BF] Prochlorperazine

4.6.BF.1] Chemotherapy-induced nausea and vomiting

a) **Diazepam** intravenously in combination with **prochlorperazine**, oral or rectal, was found to be more effective than **prochlorperazine** alone in relieving the severe nausea associated with cisplatin chemotherapy. A positive response was reported by 87% of patients which included a significant decrease

in frequency and duration of both nausea and vomiting compared with [prochlorperazine](#) alone or other antiemetic therapy [666].

b) For highly emetogenic chemotherapy (eg, cisplatin), selective serotonin 5-HT₃ receptor antagonists are the drugs of choice [666].

4.6.BG] [Promethazine](#)

4.6.BG.1] [Dyspnea](#)

a) [Promethazine](#) reduced breathlessness and improved exercise intolerance while [diazepam](#) had no effect on breathlessness, but noticeably reduced exercise tolerance in [emphysema](#) and chronic [bronchitis](#) patients. Fifteen patients completed the double-blind, placebo-controlled, crossover trial comparing [promethazine](#) 25 milligrams/day with [diazepam](#) 125 milligrams/day. [Promethazine](#) was slightly beneficial for breathlessness and exercise intolerance in pink and puffing patients with fixed [airway obstructions](#). Unlike [diazepam](#), [promethazine](#) did not affect lung function [553].

4.6.BG.2] [Insomnia](#)

a) Forty elderly patients, 20 mentally normal, randomly received [diazepam](#) 5 milligrams, [promethazine](#) 25 milligrams, [propiomazine](#) 25 milligrams, or placebo in a double-blind fashion for 21 nights. All active medications increased the duration of sleep compared with placebo. Sleep latency was shortened by all drugs in the mentally normal elderly, but [diazepam](#) was the only active agent in the psychogeriatric group. The number of awakenings was reduced by all drugs in the mentally normal subjects; however, [propiomazine](#) was the only effective agent in the psychogeriatric group. Drug hangover was the only reported adverse effect occurring in 1 [promethazine](#) patient, 1 on [propiomazine](#), and 2 on [diazepam](#) [554].

4.6.BH] [Propiomazine](#)

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

a) [Propiomazine](#) 25 milligrams (mg) was compared to [diazepam](#) 5 mg, [promethazine](#) 25 mg and placebo in a cross-over study in 40 elderly patients with insomnia. All drugs were effective in the mentally normal elderly, but in those with psychiatric problems, only [propiomazine](#) significantly reduced the number of nighttime awakenings and only [diazepam](#) shortened the sleep latency significantly. No loss of efficacy was noted with any drug over the 3 week study period and no rebound was noted following withdrawal. Psychomotor skills and serum prolactin levels were unaffected in the treatment groups [619].

4.6.BI] [Propranolol](#)

4.6.BI.1] [Alcohol withdrawal syndrome](#)

a) [Propranolol](#) has shown equivalent efficacy to [diazepam](#) in treating withdrawal symptoms in moderate, uncomplicated alcohol withdrawal, but the occurrence of [delirium](#) or seizures limits its value [653] [654].

b) [Propranolol](#) 75 milligrams/day (n=14) and [diazepam](#) 30 milligrams/day (n=13) were equally efficacious in the treatment of most acute withdrawal symptoms in a 15-day, double-blind study in 28 patients with moderate alcohol withdrawal [654]. One diazepam-treated patient dropped out because of noncompliance. There were no reported side effects or difference in sedation between the two treatment groups. As measured by the Gross Rating Scale for Alcohol Withdrawal, both drugs were equally effective in treating withdrawal symptoms, but [propranolol](#) was not effective in preventing motor seizures. One patient in the [propranolol](#) group had a major motor seizure on day 3. Bailly et al suggest that [propranolol](#) could be used to treat moderate uncomplicated alcohol withdrawal in cases where a high risk of [benzodiazepine dependence](#) exists, but [propranolol's](#) lack of anticonvulsant properties must be kept in mind.

c) Eleven of 37 subjects in a double-blind trial required no medication intervention to control alcohol withdrawal symptoms [653]. Nineteen subjects were randomized to receive oral [propranolol](#) 20 milligrams and 18 subjects to oral [diazepam](#) 10 milligrams at the first sign of withdrawal symptoms; repeat doses were given at regular intervals if symptoms persisted. In the [propranolol](#) group, one patient required [paraldehyde](#) to treat agitation and another patient had a withdrawal seizure. None of the subjects in the [diazepam](#) group experienced seizures or agitation. The author concluded that many alcohol withdrawal patients can be managed without medication. The usefulness of [propranolol](#) is limited by its lack of efficacy in preventing and/or treating seizures and [delirium](#).

4.6.BI.2] Anxiety

a) [Diazepam](#) was found to be more effective than [propranolol](#) in the treatment of the somatic symptoms of chronic anxiety [651]. However, the combination of [diazepam](#) and [propranolol](#) was more effective than either drug alone.

4.6.BI.3] Anxiety about treatment, Preoperative

a) [Propranolol](#) 80 milligrams was as effective as [diazepam](#) 10 milligrams or placebo in the treatment of preoperative anxiety in 92 females undergoing outpatient dilation and [curettage](#) for [therapeutic abortion](#) [652]. All 3 groups showed a decrease in anxiety as measured by the Spielberger [State-Trait Anxiety Inventory](#). A measure of sensory motor skills revealed that the propranolol-treated group (n=31) returned to baseline scores faster than the diazepam-treated group (n=31) or placebo group (n=30). Postoperative improvement in a test of cognitive function was seen after 2 hours in the [propranolol](#) group, after 3 hours in the placebo group, and was not apparent in the [diazepam](#) group after 3 hours. Although neither drug was superior to placebo in anxiolysis, a faster return of cognitive function was seen with [propranolol](#).

4.6.BJ] Sodium Oxybate

4.6.BJ.1] General [anesthesia](#)

a) In 20 patients (8 males and 12 females; ages 14 to 75 years) undergoing surgery, [anesthesia induction](#) with [sodium oxybate](#) (4 grams) or [diazepam](#) (10 milligrams) showed no significant difference in clinical effect, hemodynamic parameters, and blood gas changes [564].

4.6.BK] Sulpiride

4.6.BK.1] [Anxiety neurosis](#)

a) Sulpiride has offered no significant advantage over [diazepam](#) for the management of [neurotic disorders](#), including anxiety, mixed anxiety-depression, and tension. In one trial, [diazepam](#) was superior to sulpiride with regard to alleviation of anxiety, whereas sulpiride was more effective with regard to depressive symptoms and somatic complaints [511].

4.6.BL] Tandospirone

4.6.BL.1] [Neurosis](#)

a) Tandospirone appears to be similarly as effective as [diazepam](#) in the treatment of various neuroses, including [depressive neuroses](#). In a double-blind trial, 191 patients received either tandospirone 30 milligrams/day, increasing to 60 mg/day over 4 to 6 weeks or [diazepam](#) 6 milligrams/day, increasing to 12 mg/day. Of 189 evaluable patients, 46% of patients receiving tandospirone had moderate or marked improvement versus 43% of those receiving [diazepam](#). Tandospirone had a significantly better effect on

depressed mood than [diazepam](#). Anxiolytic effects of tandospirone were not observed until after at least 2 weeks of therapy [512].

4.6.BM| [Temazepam](#)

4.6.BM.1| Operation on mouth - Sedation

a) Oral [temazepam](#) is as effective as intravenous [diazepam](#) for sedation during oral surgery [562]. Thirty-nine patients were administered oral [temazepam](#) 40 milligrams with an intravenous placebo or intravenous [diazepam](#) 10 milligrams with an oral placebo. No significant difference in sedation was observed with either regimen.

4.6.BN| [Thioridazine](#)

4.6.BN.1| Anxiety

a) [Diazepam](#) was more effective for anxiety symptoms in 47 patients who were treated with [diazepam](#) 4 to 40 milligrams every day and [thioridazine](#) 20 to 200 milligrams every day to relieve mixed anxiety depressive symptoms [462].

b) In 36 patients with anxiety or depression, no difference was found between [diazepam](#) 5 to 10 milligrams 3 to 4 times daily and [thioridazine](#) 25 to 50 milligrams 3 to 4 times daily in the relief of symptoms [463].

4.6.BN.2| Behavioral syndrome

a) One study reported the superiority of oral [thioridazine](#) (10 to 200 milligrams daily) over oral [diazepam](#) (2 to 40 milligrams daily), and placebo, in the treatment of emotional and [behavioral disorders](#) in elderly, non-psychotic patients in geriatric wards, state hospitals, or nursing homes [464]. Greater improvement in the majority of symptoms assessed by the Hamilton Anxiety Scale and NOSIE were observed in patients receiving [thioridazine](#).

4.6.BO| [Tizanidine](#)

4.6.BO.1| Hemiplegia

a) In a 2-month double-blind study (n=105), [tizanidine](#) (up to 24 mg daily) was as effective as [diazepam](#) (up to 30 mg daily) in the treatment of spasticity in hemiplegia patients [488].

4.6.BO.2| Paravertebral muscle spasm

a) [Tizanidine](#) 4 to 8 mg 3 times daily has been similarly as effective as [diazepam](#) 5 to 10 mg 3 times daily in treating acute spasms of the paravertebral muscle spasms (cervical or lumbar spinal areas) in small double-blind studies [489] [490]. [Tizanidine](#) has tended to produce clinical benefit more rapidly than [diazepam](#) [489].

4.6.BP| [Triazolam](#)

4.6.BP.1| Insomnia

a) In a double-blind, randomized, 5-night, crossover study of 30 insomniacs, [triazolam](#) 0.25 milligram was superior to [diazepam](#) 5 milligrams and [triazolam](#) 0.5 milligram was superior to both 5 and 10 mg [diazepam](#) in the relief of insomnia [494].

b) [Triazolam](#) 0.5 milligram was superior to [diazepam](#) 10 milligrams with respect to number of nocturnal awakenings, total sleep time, and degree of restfulness in the morning; however, [diazepam](#) had a shorter latency to sleep onset [495].

4.6.BP.2] Preoperative sedation

a) **Triazolam** 0.25 milligram appears to be a safe, effective oral sedative agent for dental outpatients undergoing oral surgery. Less impairment in cognitive-psychomotor impairment and ambulatory function was seen after **triazolam** when compared with **diazepam** [496]. Similarly, **triazolam** 0.25 milligrams was preferred over **diazepam** 5 milligrams in 79 endodontic patients [497]. When compared to **diazepam** and placebo, **triazolam** was rated significantly better for anxiety (p less than 0.05) and for patients' rating of drug effectiveness (p less than 0.05).

b) Sublingual **triazolam** 0.2 milligram had similar anxiolytic effect and onset of effect as oral **diazepam** 10 milligrams when used as premedication for ophthalmic surgery with local **anesthesia**, but it resulted in excessive sedation in older patients [498]. This was a double-blind study in 100 patients (50 subjects in each treatment group) whose age ranged from 31 to 70 years. Both agents were efficacious and did not cause cardiovascular or other adverse effects. Sedation before, during, and after surgery was significantly greater with **triazolam** than **diazepam**. Of the 11 patients judged to be too sedated during the surgery, all were 61 years or older (mean 67 years); 10 of them received **triazolam** and 1 was in the **diazepam** group. The authors recommend that a lower dose of **triazolam** be used with older patients.

4.6.BQ] Trimeprazine

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

a) **Trimeprazine** 4 milligrams/kilogram (mg/kg) has been compared with **diazepam** 0.25 mg/kg alone or in combination with **droperidol** 0.2 mg/kg in 143 children undergoing **adenotonsillectomy** or inguinal surgery. **Trimeprazine** produced significantly more preoperative sedation and significantly less postoperative vomiting than did **diazepam**. The degree of postoperative analgesia was also enhanced. The addition of **droperidol** to either drug produced only marginal improvement in efficacy but significantly prolonged postoperative recovery time [516].

b) In a similar study comparing **diazepam** 0.5 milligrams/kilogram (mg/kg), **trimeprazine** 4 mg/kg, **pentobarbital** 3 mg/kg, and placebo in 149 children undergoing **adenotonsillectomy**, all of the drugs except placebo produced adequate sedation. No differences were noted in waking times except in the **trimeprazine** group which was significantly prolonged. The **trimeprazine** group, however, exhibited less distress in the recovery room and had half the incidence of vomiting [517].

4.6.BR] Zopiclone

4.6.BR.1] Transient insomnia

a) In a double-blind, placebo-controlled, randomized study of 100 patients (mean age 50.3 years), zopiclone 7.5 and 15 milligrams (mg) were comparable or superior to **diazepam** 10 mg and placebo for sedation the night before surgery. Sleep latency time was significantly reduced (p less than 0.05) after all drug treatments (**diazepam** -36.4%; zopiclone 7.5 mg -29.1% and zopiclone 15 mg -53.2%), but total sleep time was significantly prolonged only for zopiclone (+13.5% for 7.5 mg dose, p less than 0.05; +26.6% for 15 mg dose, p less than 0.01). The number of patients with nocturnal awakenings was greater in the placebo group (72%) and lower in the treated groups (p less than 0.01). No difference was observed between the groups regarding anxiolytic effects as observed the following morning. More adverse effects (drowsiness, dry mouth, bitter taste, headache) were observed in zopiclone 15 mg group (44%) than the zopiclone 7.5 mg (36%), **diazepam** (24%) and placebo (20%) groups (no statistical difference) [565].

6.0] References

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