

DRUGDEX-EV 0281

MICROMEDEX

DRUGDEX® Evaluations
Database updated July 2015

TEMAZEPAM

[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
Hypnotic

2) Dosing Information

a) Adult

1) Insomnia

a) 7.5 to 30 mg ORALLY at bedtime [4]

b) Pediatric

1) safety and efficacy in children under age 18 has not been established [4]

3) Contraindications

a) hypersensitivity to [temazepam](#) or benzodiazepines

b) pregnancy

4) Serious Adverse Effects

a) [Angioedema](#)

b) Complex mannerisms - behavior

c) Drug dependence

5) Clinical Applications

a) FDA Approved Indications

1j) Insomnia

1.0j Dosing Information

Drug Properties

Adult Dosage

Pediatric Dosage

1.1j Drug Properties

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

Bj) Synonyms

N-Methyloxazepam

Temazepam

1.3j Adult Dosage

1.3.1j Normal Dosage

1.3.1.Aj Oral route

1.3.1.A.1j Insomnia

aj) The recommended usual adult dose is 15 milligrams before retiring; 7.5 mg may be sufficient for some patients, while others may need 30 mg [4].

1.3.3j Dosage in Hepatic Insufficiency

Aj) CIRRHOSIS

1j) The metabolic clearance of temazepam was reportedly unaltered in the presence of cirrhosis in one study [17]. However, peak serum temazepam concentrations were achieved more slowly in cirrhotic patients as compared to normal control patients, indicating slower absorption in this patient population. Dosing adjustments do not appear required in cirrhosis, based upon these data. However, onset of sedative-hypnotic effects may be delayed.

2j) The mean clearance of temazepam was reduced in cirrhotic patients, but the amount is not significant enough to adjust the dose. Nine cirrhotic patients received temazepam 20 milligrams and blood samples were compared with healthy controls administered an equivalent dose of temazepam. No significant differences were observed between the groups, thus temazepam may be considered safe for use in patients with liver disease [18].

Bj) HEPATIC INSUFFICIENCY

1j) Among the class as a whole, LORAZEPAM, OXAZEPAM, and TEMAZEPAM may be the benzodiazepines of choice for patients with liver disease. These 3 agents undergo glucuronide conjugation and their half-lives are only slightly altered in the presence of hepatic dysfunction. Other benzodiazepines may be used, but the dosage or dosing interval may need to be altered to compensate for impaired hepatic metabolism [19] [20]; (Kraus et al, 1978) [21] [22] [23].

1.3.4] Dosage in Geriatric Patients

A) In elderly or debilitated patients, it is recommended that therapy be initiated with 7.5 milligrams until individual responses are determined [4].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Oral route

1) The safety and effectiveness in children below the age of 18 years have not been established [4].

2) [Temazepam](#) syrup has been administered to infants in doses ranging from 2.5 to 4.5 milligrams/kilogram to induce sedation prior to lung function testing. This dose was only effective in one out of six infants receiving the test. Adverse effects were frequent (3 of 6 children), including hiccoughs and irritability [16].

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

A) Onset

1) Initial Response

a) INSOMNIA, ORAL: 30 to 60 minutes [168] [169].

b) INSOMNIA, RECTAL: 2 to 4 hours [170].

2) Peak Response

a) INSOMNIA, ORAL: 50 minutes [169].

B) Duration

1) Single Dose

a) INSOMNIA, ORAL: intermediate half-life benzodiazepine [171].

b) AMNESTIC, ORAL: 4 hours [169].

2) Multiple Dose

a) Mean accumulation ratio is 1.32 [171].

2.2] Drug Concentration Levels

A) Time to Peak Concentration

1) ORAL, SOFT GELATIN CAPSULES: 0.8 hours (Fucella et al, 1977).

2) ORAL, HARD GELATIN CAPSULES: 1.4 hours (Fucella et al, 1977).

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) ORAL: Well-absorbed [172].

a) Minimal first-pass metabolism (8%) [172].

2) RECTAL: 60% to 90% [170].

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

a) 96% [172].

1) Mean free fraction is 2.6% (range 1.7 to 3.4%). Free fraction increases with age [173].

2) Cerebrospinal fluid (CSF), CSF/plasma ratio is 5.2+/-1.6 [174].

a) Plasma and cerebrospinal fluid concentrations correlate only modestly with degree of sedation [174].

B) Distribution Kinetics

1) Distribution Half-Life

a) 0.4 to 0.6 hour [172] [175].

2) Volume of Distribution

a) 1.4 L/kg [170].

1) Volume of distribution is unrelated to age or gender [173] [170].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Site not specified, 100% [172].

a) 8% metabolized during first pass [172].

B)) Metabolites

- 1)) O-conjugate of [temazepam](#), inactive [172].
- 2)) O-conjugate of the N-desmethyl derivative, inactive [172].

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

- a)) 1.0 to 1.4 mg/kg/hr [173].

2)) Renal Excretion (%)

- a)) 80% to 90% [172] [175].

3)) Clearance of total [temazepam](#) is higher in men than in women (1.35 versus 1.02 mL/min/kg). Clearance of unbound [temazepam](#) in men is higher than in women (50.5 versus 39.7 mL/min/kg), and it tends to decline with age in both sexes [173].

2.3.5] Elimination Half-life**A)) Parent Compound****1)) ELIMINATION HALF-LIFE**

- a)) 3.5 to 18.4 hours [172] [175] [176] [170].

- 1)) The half-life averaged 16.8 hours in women and 12.3 hours in men [173].

B)) Metabolites

- 1)) O-conjugate of [temazepam](#), 2 hours [175].
- 2)) O-conjugate of the N-desmethyl derivative, 2 hours [175].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.1] Contraindications

- A)) hypersensitivity to [temazepam](#) or benzodiazepines
- B)) pregnancy

3.2] Precautions

- A) addiction-prone individuals
- B) [anaphylaxis](#), possible; may occur as early as the first dose [24]
- C) [angioedema](#), possible; may occur as early as the first dose [24]
- D) chronic pulmonary insufficiency
- E) concomitant use of alcohol and other central nervous system depressants
- F) elderly and debilitated patients
- G) nursing mothers
- H) severely depressed or suicidal patients
- I) sleep-related behaviors, complex; possibility of patients performing activities while asleep, with no memory afterwards; includes sleep-driving, making phone calls, and preparing and eating food [24]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Edema

1) A 28-year-old female developed focal [rhabdomyolysis](#) following an attempted injection into the right femoral artery of [temazepam](#) 80 mg that was extracted from capsules. She presented with a macular rash, edema, and tenderness of the right leg. Within 5 days, [creatinine kinase](#) levels peaked at 25,000 international units/L (normal 10 to 90 international units/L). Aggressive diuresis (greater than or equal to 100 mL/hour) prevented permanent [sequelae](#) [27].

2) Four cases of intraarterial injection of the contents of [temazepam](#) capsules have been reported. Because of [temazepam's](#) gel formulation, intraarterial injection injures vascular endothelium. [Thrombosis](#), edema, ischemia, and [muscle necrosis](#) all leading to [rhabdomyolysis](#) have occurred. Treatment recommendations include heparinization and [forced diuresis](#) [28].

3.3.1.B] Hypotension

1) [Temazepam](#) resulted in a decrease in blood pressure when supine or standing in a study of twelve healthy, elderly subjects were administered either [temazepam](#) 15 mg, [temazepam](#) 30 mg, or placebo. Orthostatic blood pressure and heart rate were measured in each subject. There was a significant fall in blood pressure and heart rate in both the supine and standing positions [26].

3.3.1.C] Ischemia

1) Four cases of intraarterial injection of the contents of [temazepam](#) capsules have been reported. Because of [temazepam's](#) gel formulation, intraarterial injection injures vascular endothelium. [Thrombosis](#), edema, ischemia, and [muscle necrosis](#) all leading to [rhabdomyolysis](#) have occurred. Treatment recommendations include heparinization and [forced diuresis](#) [28].

3.3.1.D] Palpitations

1) Palpitations have been reported in 0.5% to 0.9% of patients treated with [temazepam](#) in clinical trials [25].

3.3.1.E] [Thrombosis](#)

1) Four cases of intraarterial injection of the contents of [temazepam](#) capsules have been reported. Because of [temazepam's](#) gel formulation, intraarterial injection injures vascular endothelium. [Thrombosis](#), edema, ischemia, and [muscle necrosis](#) all leading to [rhabdomyolysis](#) have occurred. Treatment recommendations include heparinization and [forced diuresis](#) [28].

3.3.2] Dermatologic Effects

3.3.2.A] Diaphoresis

1) Hyperhidrosis has occurred in 0.5% to 0.9% of patients treated with [temazepam](#) in clinical trials [25].

3.3.4] Gastrointestinal Effects

3.3.4.A] Diarrhea

1) Incidence: 1.7% [25]

2) Diarrhea has been reported in 1.7% of patients treated with [temazepam](#) (n=1076) compared with 1.1% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.4.B] Nausea

1) Incidence: 3.1% [25]

2) Nausea has been reported in 3.1% of patients treated with [temazepam](#) (n=1076) compared with 3.8% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.7] Immunologic Effects

3.3.7.A] Anaphylaxis

1) Incidence: rare [25]

2) Cases of [angioedema](#) involving the tongue, glottis, or larynx, some fatal, have been reported rarely in patients following the first or subsequent dose of sedative-hypnotics, including [temazepam](#). Additional symptoms suggestive of [anaphylaxis](#), including dyspnea, throat closing, or nausea and vomiting, have been reported. Some patients with these symptoms have presented to the emergency department. Do not rechallenge patients who have experienced [angioedema](#) following [temazepam](#) treatment [25].

3.3.8] Musculoskeletal Effects

3.3.8.A] Asthenia

1) Incidence: 1.4% [25]

2) Weakness has been reported in 1.4% of patients treated with [temazepam](#) (n=1076) compared with 0.9% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.8.B] Backache

1) Incidence: 0.5% to 0.9% [25]

2) Backache has occurred in 0.5% to 0.9% of patients treated with [temazepam](#) in clinical trials [25].

3.3.8.C] Muscle necrosis

1) Four cases of intraarterial injection of the contents of [temazepam](#) capsules have been reported. Because of [temazepam's](#) gel formulation, intraarterial injection injures vascular endothelium. [Thrombosis](#), edema, ischemia, and [muscle necrosis](#) all leading to [rhabdomyolysis](#) have occurred. Treatment recommendations include heparinization and [forced diuresis](#) [28].

3.3.8.D] Rhabdomyolysis

1) A 28-year-old female developed focal [rhabdomyolysis](#) following an attempted injection into the right femoral artery of [temazepam](#) 80 mg that was extracted from capsules. She presented with a macular rash, edema and tenderness of the right leg. Within 5 days, [creatinine kinase](#) levels peaked at 25,000 international units/liter (L) (normal 10 to 90 international units/L). Aggressive diuresis (greater than or equal to 100 milliliters/hour) prevented permanent [sequelae](#) [27].

2) Four cases of intraarterial injection of the contents of [temazepam](#) capsules have been reported. Because of [temazepam's](#) gel formulation, intraarterial injection injures vascular endothelium. [Thrombosis](#), edema, ischemia, and [muscle necrosis](#) all leading to [rhabdomyolysis](#) have occurred. Treatment recommendations include heparinization and [forced diuresis](#) [28].

3.3.9] Neurologic Effects

3.3.9.A] Amnesia

1) Incidence: less than 0.5% [25]

2) Amnesia has been reported in less than 0.5% of patients treated with [temazepam](#) during clinical trials; amnesia may occur unpredictably [25].

3.3.9.B] Confusion

1) Incidence: 1.3% [25]

2) Confusion has been reported in 1.3% of patients treated with [temazepam](#) (n=1076) compared with 0.5% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.C] Dizziness

1) Incidence: 4.5% [25]

2) Dizziness has been reported in 4.5% of patients treated with [temazepam](#) (n=1076) compared with 3.3% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.D] EEG finding

1) [Temazepam](#) has affected the [electroencephalogram](#) (EEG) during closed eyes conditions. Ten healthy subjects were administered either [temazepam](#) 20 mg or a placebo with EEGs measured before and after each dose. A decrease in power between the 7- to 12-Hertz frequency and an increase in the 12-to 25-Hertz region were observed at 1 and 3 hours after administration, respectively. The most prominent effects were noted at the 1 hour mark [33].

3.3.9.E] Fatigue

1) Incidence: 4.8% [25]

2) Fatigue has been reported in 4.8% of patients treated with [temazepam](#) (n=1076) compared with 4.7% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.F] Hangover

1) Incidence: 2.5% [25]

2) Hangover has been reported in 2.5% of patients treated with [temazepam](#) (n=1076) compared with 1.1% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.G] Headache

1) Incidence: 8.5% [25]

2) Headache has been reported in 8.5% of patients treated with [temazepam](#) (n=1076) compared with 9.1% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.H] Impaired cognition

1) [Temazepam](#) doses of 20 mg have been associated with mild impairment of cognitive function and psychomotor performance only during the first hour after administration [30]. Doses up to 30 mg produced a slightly increased impairment of early morning psychomotor performance. A pronounced hangover was observed at [temazepam](#) 40 mg and 60 mg doses. An increase in beta waves observed on the [electroencephalogram](#) correlated with the occurrence of hangover [31].

2) [Temazepam](#) induced greater cognitive dysfunction compared with placebo following [anesthesia](#) with [alfentanil](#) and [propofol](#). Fifty-five patients were administered either placebo (n=19) or [temazepam](#) 20 mg (n=36) prior to [anesthesia](#). Cognitive skills, including attention and memory, were assayed by computer techniques. A significant impairment was observed in the [temazepam](#) group at 30 minutes after surgery, but normalization began to occur at approximately 4 hours [32].

3.3.9.I] Lethargy

1) Incidence: 4.5% [25]

2) Lethargy has been reported in 4.5% of patients treated with [temazepam](#) (n=1076) compared with 3.4% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.9.J] Rebound insomnia

1) Rebound insomnia was reported in patients with insomnia at baseline (n=18) who were treated with [temazepam](#). Following 4 nights in a sleep lab to assess baseline sleep parameters, [temazepam](#) 30 mg, [triazolam](#) 0.5 mg, or placebo were administered on 3 to 4 consecutive nights, withdrawn for 2 nights, given on 1 additional night, then withdrawn. During the first withdrawal period, [temazepam](#) did not produce a rebound insomnia. Upon the second and final withdrawal of [temazepam](#), total wake time increased significantly and sleep time decreased significantly compared to baseline [29].

3.3.9.K] Somnolence

1) Incidence: 9.1% [25]

2) Drowsiness has been reported in 9.1% of patients treated with [temazepam](#) (n=1076) compared with 5.6% of patients treated with placebo (n=783) during clinical trials [25].

3.3.9.L] Vertigo

1) Incidence: 1.2% [25]

2) Vertigo has been reported in 1.2% of patients treated with [temazepam](#) (n=1076) compared with 0.8% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.10] Ophthalmic Effects

3.3.10.A] Blurred vision

1) Incidence: 1.3% [25]

2) Blurred vision has been reported in 1.3% of patients treated with [temazepam](#) (n=1076) compared with 1.3% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.10.B] Burning sensation in eye

1)) Incidence: 0.5% to 0.9% [25]

2)) Burning eyes have been reported in 0.5% to 0.9% of patients treated with [temazepam](#) during controlled clinical trials [25].

3.3.10.C) Horizontal nystagmus

1)) Incidence: less than 0.5% [25]

2)) [Horizontal nystagmus](#) has been reported in less than 0.5% of patients treated with [temazepam](#) during controlled clinical trials [25].

3.3.12) Psychiatric Effects

3.3.12.A) Aggressive behavior

1)) Behavioral changes characterized by aggression, bizarre behavior, agitation, hallucinations, and depersonalization, have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed [25].

3.3.12.B) Agitation

1)) Incidence: less than 0.5% [25]

2)) Agitation has been reported in less than 0.5% of patients treated with [temazepam](#) during controlled clinical trials. Behavioral changes characterized by aggression, bizarre behavior, agitation, hallucinations, and depersonalization, have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed [25].

3.3.12.C) Anxiety

1)) Incidence: 2% [25]

2)) Anxiety has been reported in 2% of patients treated with [temazepam](#) (n=1076) compared with 1.5% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.12.D) Bizarre behavior

1)) Behavioral changes characterized by aggression, bizarre behavior, agitation, hallucinations, and depersonalization, have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed [25].

3.3.12.E) Complex mannerisms - behavior

1)) Complex behaviors including sleep driving, preparing and eating food, making phone calls, or having sexual intercourse while not fully awake and subsequently not remembering the performance of these activities has occurred following administration of sedative-hypnotics. These behaviors have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed.

In cases of sleep-driving, strongly consider discontinuation of [temazepam](#) due to the risk to the patient and others [25].

3.3.12.F] Depersonalization

1) Behavioral changes characterized by aggression, bizarre behavior, agitation, hallucinations, and depersonalization, have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed [25].

3.3.12.G] Depression

1) Incidence: 1.7% [25]

2) Depression has been reported in 1.7% of patients treated with [temazepam](#) (n=1076) compared with 1.8% of patients treated with placebo (n=783) during controlled clinical trials. In patients with preexisting depression, worsening of depression, including suicidal thinking, has been reported in association with sedative-hypnotic use [25].

3.3.12.H] Euphoria

1) Incidence: 1.5% [25]

2) Euphoria has been reported in 1.5% of patients treated with [temazepam](#) (n=1076) compared with 0.4% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.12.I] Feeling nervous

1) Incidence: 4.6% [25]

2) Fatigue has been reported in 4.6% of patients treated with [temazepam](#) (n=1076) compared with 8.2% of patients treated with placebo (n=783) during controlled clinical trials [25].

3.3.12.J] Hallucinations

1) Incidence: less than 0.5% [25]

2) Hallucinations have been reported in less than 0.5% of patients treated with [temazepam](#) during controlled clinical trials. Behavioral changes characterized by bizarre behavior, agitation, hallucinations, and depersonalization, have occurred in sedative-hypnotic naive and sedative-hypnotic experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed [25]. [25].

3) An unusual case of musical hallucinations was reported in an elderly woman with preexisting tinnitus following initiation of unspecified doses of [lorazepam](#) as an anxiolytic and [temazepam](#) as a hypnotic. The hallucinations consisted of popular songs and hymns and were associated with hyperacusis. Hallucination intensity was reduced following discontinuation of [temazepam](#) and dosage reduction of [lorazepam](#); all symptoms disappeared following substitution with [chloral hydrate](#) [34].

3.3.15] Respiratory Effects

3.3.15.A] Dyspnea

1) Incidence: 0.5% to 0.9% [25]

2) Dyspnea has been reported in 0.5% to 0.9% of patients treated with [temazepam](#) in clinical trials [25].

3.3.16] Other

3.3.16.A] Angioedema

1]) Incidence: rare [25]

2]) Cases of [angioedema](#) involving the tongue, glottis, or larynx, some fatal, have been reported rarely in patients following the first or subsequent doses of sedative-hypnotics, including [temazepam](#). Additional symptoms suggestive of [anaphylaxis](#), including dyspnea, throat closing, or nausea and vomiting, have been reported. Some patients with these symptoms have presented to the emergency department. Do not rechallenge patients who have experienced [angioedema](#) following [temazepam](#) treatment [25].

3.3.16.B] Drug dependence

1]) Drug abuse and dependence has been reported with [temazepam](#) use. Use caution in administering [temazepam](#) to patients with a history of drug abuse; these patients may increase dose on their own. Limit repeated prescriptions when there is not adequate medical supervision [25]

3.3.16.C] Drug withdrawal

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.D] Withdrawal sign or symptom

1]) After abrupt discontinuation, withdrawal symptoms similar to those reported with barbiturates and alcohol use, including convulsions, tremor, abdominal and muscle cramps, vomiting, and sweating, have occurred. More severe withdrawal symptoms have been limited to patients receiving excessive doses over an extended period of time. Milder withdrawal symptoms including [dysphoria](#) and insomnia have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Avoid abrupt discontinuation and follow a gradual dosage tapering schedule following extended therapy at [temazepam](#) doses higher than 15 mg. Use caution in administering [temazepam](#) to patients with a history of drug abuse; these patients may increase dose on their own. Limit repeated prescriptions when there is not adequate medical supervision [25].

2]) A planned dose-reduction withdrawal program called "Planpak" was successful in 52% of 44 patients who had been taking [temazepam](#) nightly for 2 months to 8 years. The dose of [temazepam](#) was reduced every 2 weeks from 10 mg to 5 mg to 2 mg. Six weeks after starting the dose reduction, patients were withdrawn completely. Successful outcome was defined as being hypnotic-free at 3 to 6 months after discontinuing [temazepam](#). Only 9% of patients experienced a significant withdrawal reaction [35].

3]) Benzodiazepine withdrawal symptoms have been reported in patients who received a short-acting benzodiazepine in substitution for a long-acting benzodiazepine. 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 [36].

4]) Three days after discontinuing [temazepam](#), a 22-year old male demonstrated moderate withdrawal symptoms including anxiety, tension, restlessness, insomnia, and lack of appetite. He had increased his [temazepam](#) dose to 100 mg daily. The patient was withdrawn uneventfully using clomethiazole [37].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

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

a)) Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

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)) All benzodiazepines can be expected to cross the placenta. **Teratogenicity** with **temazepam** has not been confirmed; however, other benzodiazepines have demonstrated teratogenic potential [161]. Thus, use of **temazepam** during pregnancy is not recommended. If pregnancy occurs during chronic use, the patient should be advised of the desirability of discontinuing the drug and of possible consequences to the fetus. If given, prescribe as monotherapy in the lowest effective dosage, for the shortest duration possible, and in divided doses to avoid high peak concentrations [162]. In contrast to benzodiazepines, the non-benzodiazepines **zolpidem** and **zaleplon** are in Pregnancy Risk Categories B and C, respectively [163] [164].

5)) Literature Reports

a)) **Temazepam** is a metabolite of **diazepam**; as such, these agents may have similar reproductive effects and **diazepam** is among the most well studied for intrauterine exposure effects of benzodiazepines. To date, evidence is conflicting and inconsistently supports an increased risk of **congenital malformations** with intrauterine **diazepam** exposure. Researchers described 8 infants exposed to **diazepam** 30 mg/day or more, or **oxazepam** 75 mg/day or more throughout gestation who exhibited **dysmorphic features**, **growth retardation**, and central nervous system defects; the authors suggested probable effects of benzodiazepine use [148] [149]. Several studies and case reports have also suggested a higher incidence of oral clefts and other **congenital malformations** among infants born to mothers who used **diazepam** during the first trimester of pregnancy [150] [151] [152]. However, such data is countered by other evidence where **diazepam** exposure was not clearly associated with **teratogenic effects** [153] [154] [155] [156].

b)) In a retrospective case control study of 43 pregnant Hungarian women who attempted suicide with nitrazepam or other benzodiazepines (mean nitrazepam dose 204 mg) between 1960 and 1993, 13 of their exposed children were born with congenital abnormalities (30.2%) compared with 3 of their unexposed siblings (10.3%, n=29) (odds ratio 3.8, 95% confidence interval, 1 to 14.6). Congenital abnormalities (CAs) were present in 7 children exposed to nitrazepam alone or with other drugs between postconception weeks 3 and 12, including 3 cases of **congenital inguinal hernia**, 1 case of torticollis, 1 case of **pectus excavatum**, complex CA of the respiratory system, and 1 case of multiple CAs with **talipes equinovarus**, mild **microcephaly**, and 5 other mild anomalies and borderline fetal alcohol syndrome (FAS). CAs that occurred in the 6 children exposed after postconception week 12 included 2 cases of **congenital inguinal hernia**, 1 case of bronchial stenosis,

and 3 cases of multiple CAs, including FAS with [talipes equinovarus](#) and low IQ; borderline FAS with mild [microcephaly](#) and [talipes equinovarus](#) with 11 minor abnormalities; and [talipes equinovarus](#) with 4 minor abnormalities. Their unexposed siblings with CAs were affected with [cleft lip and palate](#), [ventricular septal defect](#), and FAS. Most CAs were classified as mild deformations. Researchers note concomitant exposure to other drugs, tobacco smoke, and alcohol in several of the exposed children as potential confounds [157].

c) Mixed results were found in a meta-analysis of cohort and case-control studies that reported on the occurrence of major malformations in infants exposed to any benzodiazepine during at least the first trimester of pregnancy [158]. When only cohort studies were pooled, no significant association between benzodiazepine use and major malformations was noted (odds ratio 0.90; 95% confidence interval 0.61 to 1.35; $p=0.62$); data pooled from case-control studies, however, showed a positive association with major malformations (odds ratio 3.01; 95% confidence interval 1.32 to 6.84; $p=0.008$). Similar observations were made with regard to oral cleft; the pooled cohort study data did not substantiate an association with drug use (odds ratio 1.19; 95% confidence interval 0.34 to 4.15; $p=0.997$), whereas the case-controlled data did (odds ratio 1.79; 95% confidence interval 1.13 to 2.82; $p=0.01$). Finally, the meta-analysis found two case-control studies that each provided conflicting evidence of any association between benzodiazepine exposure and cardiac malformations, and one study failed to find an association between exposure and central nervous system defects.

d) A possible drug interaction between [temazepam](#) and [diphenhydramine](#) resulting in the stillbirth of a term infant who, on the previous day, was in no apparent distress has been reported [159]. The 28-year-old mother had taken 50 mg of [diphenhydramine](#) followed by 30 mg of [temazepam](#) 90 minutes later. Approximately 3 hours post-dose, the patient experienced violent intrauterine fetal movements lasting several minutes, then abruptly abating. The stillborn infant was delivered 4 hours later. The authors also reported an 81% (51/63) fetal mortality rate when administering the concomitant agents to pregnant rabbits.

e) Neonatal withdrawal symptoms following maternal ingestion have been associated with [diazepam](#), of which [temazepam](#) is a metabolite [160]. Symptoms included tremors, irritability, hyperactivity, hypertonicity, tachypnea, vigorous sucking, and in one case, weight loss, loose stools and vomiting; withdrawal symptoms may not be evident until several days after birth.

B) Breastfeeding

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

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

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

3) Clinical Management

a) Human data is limited regarding the use of [temazepam](#) during breastfeeding; caution is advised. While the American Academy of Pediatrics identifies a number of benzodiazepines as having unknown effects of possible concern to a nursing infant [165], the World Health Organization

considers [diazepam](#) safe during lactation when used occasionally in small doses [167]. [Temazepam](#) is a metabolite of [diazepam](#).

4) Literature Reports

a) Milk and plasma samples from 10 breastfeeding women receiving [temazepam](#) 10 to 20 mg showed that it was passed into breast milk, with a milk:plasma ratio of 0.12 [166]. In the infants, [temazepam](#) was undetectable in plasma and no adverse effects were noted.

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.12 [166]

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 [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].

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 [61].

3.5.1.B] [Amobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].

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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.C] Anileridine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.D] Aprobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.E] Buprenorphine

1) Interaction Effect: increased risk of [respiratory depression](#)

2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing dose of one or both agents [65].

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 [65].

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

3.5.1.F] Butabarbital

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].

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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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

[73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.G] [Butalbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.H] [Carbinoxamine](#)

- 1) Interaction Effect: additive CNS effects
- 2) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects [105] [106]. 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 [105] [106]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 7) Probable Mechanism: additive effects on the CNS

3.5.1.I] [Carisoprodol](#)

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

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.J] [Chloral Hydrate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: [Chloral](#) hydrate, with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [121]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.K] [Chlorzoxazone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [128] [129] [130] [131].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.L] [Codeine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.M) [Dantrolene](#)

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

- 1)) Interaction Effect: decreased [temazepam](#) effectiveness
- 2)) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3)) Severity: minor
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7)) Probable Mechanism: increased [temazepam](#) clearance
- 8)) Literature Reports

a)) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.O) [Dienogest](#)

- 1)) Interaction Effect: decreased [temazepam](#) effectiveness
- 2)) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3)) Severity: minor
- 4)) Onset: delayed
- 5)) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.P] Dong Quai

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

2) Summary: Dong quai extract inhibited metabolism of [diazepam](#) and increased its muscle relaxant effect in rats [123]. 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](#) [123]. It is suspected that dong quai may affect other drugs metabolized by the cytochrome P450 enzymes which metabolize [diazepam](#). Caution is advised.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

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

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

8) Literature Reports

a) *Angelica dahurica* (dong quai) extract 1 gram/kilogram orally increased the maximum concentration of oral [diazepam](#), yet did not alter pharmacokinetics of intravenous (IV) [diazepam](#) in rats. [Diazepam](#) 5 milligrams/kilogram (mg/kg) was administered orally to rats alone, and one hour after dong quai extract. When administered alone, only the maximum concentration (C_{max}) of [diazepam](#) could be calculated, as the plasma concentration of [diazepam](#) was undetectable at all sample time points except for 2 hours. After dong quai, [diazepam](#) C_{max} increased from 23.0 +/- 12.4 nanograms/milliliter (ng/mL) to 92.1 +/- 50.3 ng/mL (p less than 0.05). [Diazepam](#) pharmacokinetics were not significantly changed by dong quai when [diazepam](#) was administered intravenously. [Diazepam](#) is metabolized by CYP2C11- and CYP2D1-mediated demethylation, CYP3A2-mediated hydroxylation, and CYP2D1-mediated 4'-hydroxylation. Dong quai extract inhibited all of these isoenzymes [122].

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 [122].

3.5.1.Q| Drospirenone

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.R| Estradiol Cypionate

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.S| Estradiol Valerate

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and

determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.T) [Ethchlorvynol](#)

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

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

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: CNS depression

3.5.1.U) [Ethinyl Estradiol](#)

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

2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.V] Ethynodiol Diacetate

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.W] Etonogestrel

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.X] 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 [118]. 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](#) [64]. 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 [118].

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 [118].

7) Probable Mechanism: additive CNS depression

3.5.1.Y] [Flumazenil](#)

1) Interaction Effect: precipitation of seizures

2) Summary: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [54].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [flumazenil](#) and benzodiazepines is contraindicated in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Abrupt discontinuation of the protective effect of a benzodiazepine agonist can cause seizures in epileptic patients [54].

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

3.5.1.Z] [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 [38]. 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.AA] [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 [137].

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 [137].

7) Probable Mechanism: additive CNS depression

3.5.1.AB] [Hydromorphone](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].

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 [61].

3.5.1.AC] [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](#) [93]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [94].

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 [92].

3.5.1.AD] [Levonorgestrel](#)

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AE] [Levorphanol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.AF] [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 [119] and use with caution [120].
- 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 [119] and use with caution [120].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AG] Magnolia

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [100] [101] [102]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [103]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [104]. 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 [95].

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 [96].

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 [97].

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) [98].

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 [99].

3.5.1.AH] [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](#) [114] [115] [116] 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](#) [114] [115] [116] 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.AI] [Medroxyprogesterone Acetate](#)

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AJ] [Meperidine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.AK] [Mephenesin](#)

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

7J) Probable Mechanism: CNS depression

3.5.1.ALJ **Mephobarbital**

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

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

7J) Probable Mechanism: CNS depression

8J) Literature Reports

aJ) It has been noted in several studies that combinations of **clonazepam** and **primidone** or **phenobarbital** tend to produce more severe side effects (drowsiness, irritability, hyperactivity), while **clonazepam** in combination with hydantoins or **carbamazepine** are better tolerated [67] [68] [69] [70] [71].

bJ) Concomitant administration of intravenous **midazolam** and **thiopental** resulted in synergistic (supraadditive) effects during **induction of anesthesia** [72]. 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 [73]. A 15% reduction in the **thiopental** induction dose requirement has been observed if it follows intramuscular premedication with **midazolam** [74]. The interaction between **midazolam** and **thiopental** may in part be dependent on **thiopental** dosing [75].

3.5.1.AMJ **Meprobamate**

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [128] [129] [130] [131].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

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

7J) Probable Mechanism: CNS depression

3.5.1.ANJ **Mestranol**

1J) Interaction Effect: decreased **temazepam** effectiveness

2J) Summary: Combination contraceptives may stimulate the glucuronide conjugation of **temazepam** [135] and increase the clearance of **temazepam** [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and **temazepam** for a reduced response to the benzodiazepine should be considered.

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AO| [Metaxalone](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [128] [129] [130] [131].

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.AP| [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 [60].

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 [60].

7) Probable Mechanism: additive CNS depression effects

3.5.1.AQ| [Methocarbamol](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [128] [129] [130] [131].

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.AR] [Methohexital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.AS] [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 [66].
- 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 [66].
- 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 [66].

3.5.1.AT] [Morphine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

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

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.AV] [Norelgestromin](#)

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AW] [Norethindrone](#)

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

2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AX] [Norgestimate](#)

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

2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).

7) Probable Mechanism: increased [temazepam](#) clearance

8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AY] [Norgestrel](#)

- 1) Interaction Effect: decreased [temazepam](#) effectiveness
- 2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of [temazepam](#) [135] and increase the clearance of [temazepam](#) [133]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to the benzodiazepine should be considered.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Concomitant use of [temazepam](#) and combination contraceptives may increase [temazepam](#) clearance [133]. Consider monitoring patients receiving concurrent combination contraceptives and [temazepam](#) for a reduced response to [temazepam](#).
- 7) Probable Mechanism: increased [temazepam](#) clearance
- 8) Literature Reports

a) Concomitant oral contraceptive and [temazepam](#) therapy has been reported to alter the metabolism of [temazepam](#). In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of [temazepam](#) following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of [temazepam](#) may be less effective in women using oral contraceptives [134].

3.5.1.AZ] [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 [110] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [111].
- 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 [110] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [111].
- 7) Probable Mechanism: additive effects

3.5.1.BA] [Oxymorphone](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].

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 [61].

3.5.1.BB| 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 [82]. 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 [82]. 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 [82].

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 [107]. 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 [108]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [109].

3.5.1.BC] Pentobarbital

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].

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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous midazolam and thiopental resulted in synergistic (supraadditive) effects during induction of anesthesia [72]. 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 [73]. A 15% reduction in the thiopental induction dose requirement has been observed if it follows intramuscular premedication with midazolam [74]. The interaction between midazolam and thiopental may in part be dependent on thiopental dosing [75].

3.5.1.BD] 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 [132].

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 [132].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BE] Phenobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.BF] Primidone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.BG| [Propoxyphene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.BH| [Remifentanyl](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].
- 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 [61].

3.5.1.BI] 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 [139].
- 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.BJ] Secobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].
- 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 [67] [68] [69] [70] [71].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.BK] 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 [126] [127]. 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 [124].

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 [125].

3.5.1.BL] Sodium Oxybate

- 1) Interaction Effect: additive respiratory depression
- 2) Summary: In trials involving sodium oxybate, respiratory depression was reported [39]. 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.BM] 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 [55] [56] [57] [58]. St. John's wort did not, however, significantly affect quazepam efficacy [55]. 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 [55] [56] [57] [58]. 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 [55].

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) [56].

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 [59].

d) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term

study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and Cmax of oral [midazolam](#) were reduced by 50%, and oral clearance increased 2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [57].

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) [58].

3.5.1.BN] [Sufentanil](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [62]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [63]. 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](#) [64].

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 [61].

3.5.1.BO] [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 [81].

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 [81].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BP| 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 [113]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [113]. 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) [112]. 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](#) [112].

3.5.1.BQ| 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 [117].
- 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 [117].
- 7) Probable Mechanism: additive effects

3.5.1.BR] 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 [91]. 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 [91]. 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 [91].

3.5.1.BS] Theophylline

- 1) Interaction Effect: decreased benzodiazepine effectiveness
- 2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [49] [50] [51] [52]. 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 [53].
- 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 [40].

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 [41]. Other studies and case reports have also shown that [theophylline](#) antagonizes the sedative effects of [diazepam](#) [42] [43].

c)) Three case reports described patients who had the sedative effects of [lorazepam](#) reversed postoperatively by the administration of [aminophylline](#) 1 mg/kg intravenously [44]. This same [aminophylline](#) dose was used to reverse the sedative effects of [midazolam](#) in three other patients [45]. [Theophylline](#) also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [46].

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 [47].

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 [48].

3.5.1.BT] Thiopental

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

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [76] [77] [78] [79] [80].

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 [67] [68] [69] [70] [71].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [72]. 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 [73]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [74]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [75].

3.5.1.BU] 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 [82]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [90] [83]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [83]. 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 [82]. 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 [82] [83]. 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 [82].

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 [84] [85]. 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 [86]. 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 [87]. 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 [88].

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 [89].

3.5.1.BV] 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 [138].
- 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 [138].
- 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 temazepam
- 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 [143] [144] [145].

3J) Severity: minor

4J) Onset: rapid

5J) Substantiation: probable

6J) Clinical Management: Monitor benzodiazepine response for desirable outcome. Reduction or elimination of [caffeine](#) exposure would be expected to restore desirable sedative effects (nighttime sedation).

7J) Probable Mechanism: central nervous system antagonistic effects

8J) Literature Reports

aJ) 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 [142].

3.5.2.BJ Ethanol

1J) Interaction Effect: impaired psychomotor functions

2J) Summary: In a controlled study of six healthy volunteers, coadministration of ethanol with [temazepam](#) resulted in significantly impaired divided attention tests, tracking tests, and reaction time tests over a 3-hour period. There was also significant impairment for each drug alone versus placebo on some tests [141].

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: probable

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

7J) Probable Mechanism: additive CNS depression

8J) Literature Reports

aJ) The effects of concurrent [temazepam](#) and ethanol administration on the psychomotor performance of six healthy volunteers were examined in a double-blind, crossover study. Subjects received each of four treatments, including placebo drink plus placebo capsule, placebo drink plus 15 mg [temazepam](#), ethanol-containing drink plus placebo capsule, and ethanol-containing drink plus 15 mg [temazepam](#). The dose of ethanol was calculated to achieve a concentration of 11 mmol/L, based on the subject's lean body mass. Thirty minutes after treatment, the subjects began taking psychomotor tests alternating with rest periods, during which blood, urine, and breath samples were obtained. Results showed that [temazepam](#), especially when combined with ethanol, caused impairment as measured by tracking tasks over three hours. Of special interest was that the subjects did not perceive their performance to be impaired after taking both ethanol and [temazepam](#) [140].

4.0J Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1] Monitoring Parameters

A]) Therapeutic

1]) Physical Findings

a]) Monitor for improvement in onset and duration of sleep following 7 to 10 days of treatment.

B]) Toxic

1]) Physical Findings

a]) Monitor for complex behaviors ("sleep-driving" or preparing or eating food, making phone calls, or having sex while not fully awake). These may be indicative of a previously undiagnosed psychiatric or physical disorder.

b]) Monitor for signs and symptoms of serious [hypersensitivity reactions](#), including [anaphylaxis](#) and [angioedema](#) involving the tongue, glottis, or larynx.

c]) Assess for emergence of worsening of insomnia, tolerance, or adaptation to the effects of [temazepam](#) (ie, increased wakefulness during the last third of the night and development of increased daytime anxiety) following several weeks of nightly use.

d]) Monitor for emergence of mental or behavioral abnormalities (ie, decreased inhibition, aggressiveness, extroversion, bizarre behavior, agitation, hallucinations, and depersonalization). These may be indicative of a previously undiagnosed psychiatric or physical disorder.

e]) Evaluate for oversedation, dizziness, confusion, or ataxia, especially in elderly or debilitated patients.

f]) Monitor for signs and symptoms of worsening depression (including suicidal thinking) in primarily-depressed patients.

4.2] Patient Instructions

A]) [Temazepam](#) (By mouth)

[Temazepam](#)

Treats insomnia.

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 [temazepam](#) or if you are pregnant.

How to Use This Medicine:

Capsule, Tablet

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

Take this medicine just before bedtime, or when you are having trouble falling asleep. You should not take this medicine if you do not have 7 to 8 hours to sleep or rest before you need to be active again.

Call your doctor if you still have trouble sleeping after you take this medicine for 7 to 10 days. This medicine is not for long-term use.

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

Use this medicine only when you cannot sleep. You do not need to take it on a schedule.

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

Drugs and Foods to Avoid:

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

This medicine can intensify the effects of alcohol, sedatives, tranquilizers, and narcotic pain medicine. Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Warnings While Using This Medicine:

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 breathing problems or lung disease, liver disease, [kidney disease](#), a history of depression or mental illness, or if you have been addicted to alcohol or other drugs.

This medicine can cause a serious [allergic reaction](#).

This medicine may cause you to do things while you are still asleep that you may not remember the next morning, such as driving a car, having sex, or eating. Tell your doctor right away if you learn that this has happened.

This medicine may make you dizzy or drowsy, especially first thing the next morning. Do not drive or do anything that could be dangerous until you know how this medicine affects you.

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.

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

Anxiety, depression, unusual behavior, or thoughts of hurting yourself

Fast or pounding heartbeat

Memory loss, or seeing, hearing, or feeling things that are not there

Seizures

Severe confusion, drowsiness, or muscle weakness

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

Drowsiness

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

4.3] Place In Therapy

A) [Temazepam](#) is indicated for the short-term treatment of insomnia [188]. When given 30 minutes before bedtime, it improves total sleep time, sleep latency, and number of awakenings. It is also effective in reducing early morning awakening which is frequently seen in the geriatric patient. 2. Similar to other benzodiazepines, [temazepam](#) has also been effective in the treatment of anxiety.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) **Temazepam**, a minor metabolite of **diazepam**, is a 1,4 benzodiazepine with prominent hypnotic properties, primarily improving parameters of sleep maintenance with little effect on sleep induction. **Temazepam** decreases the amplitude of cortical somatosensory-evoked potentials in the EEG, allowing for decreased interruption in sleep [177].

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 pharmacologic 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 [178] [179].

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 [180].

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 [181].

5) **Temazepam** has no objective effect on sleep onset latency, but does produce a significant reduction in self-assessed sleep latency [182]. Total sleep time is increased, mostly due to an increase in stage 2 (non-REM) sleep and decrease in nocturnal awakenings. There is no decreased proportion of REM sleep, but the onset of the first REM period is delayed. Both stages 3 and 4 are decreased. In neurotic patients or patients with **endogenous depression**, the decrease in stages 3 and 4 is accompanied by a decrease in night terrors and nightmares. Following several weeks of therapy, there is a trend toward a rebound effect resulting in increased sleep latency [183].

B) REVIEW ARTICLES

1) The use of **temazepam** and other short-acting benzodiazepines for treating insomnia has been reviewed [184].

2) The efficacy and withdrawal effects of hypnotics, including **temazepam** have been reviewed [185].

3) The clinical trials of hypnotics, including **temazepam**, have been reviewed [186].

4) The place in therapy of hypnotics, including **temazepam**, has been reviewed [187].

4.5] Therapeutic Uses

4.5.A] Anxiety

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:

Limited data suggest the efficacy of [temazepam](#) for anxiety [1] [2] [3]

3) Adult:

a) [Temazepam](#) in doses ranging from 30 to 90 milligrams/day has been used in the treatment of anxiety in association with other disorders including [psychoneuroses](#) and depression. Results from limited data indicate that this drug may have some therapeutic benefit based on self-grading scales, global indexes, and clinical symptom improvement. The drug is associated with only minor side effects which include dry mouth and drowsiness [1] [2] [3].

4.5.B) [Dementia](#)

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

4.5.C) [Insomnia](#)

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:

[Temazepam](#) is indicated for the short-term treatment of insomnia (generally 7 to 10 days) [4]

3) Adult:

a) General

1) [Temazepam](#) has been successfully used in doses of 7.5 to 30 milligrams to induce sleep with minimal adverse reactions (ie, hypnotic hangover). Results from most studies indicate that the drug can improve sleep patterns with a reduction in latency time and waking periods during the night with no action on early morning awakening [5] [6] [7] [8] [9] [10]. Patients using [temazepam](#) for more than 2 to 3 weeks should undergo periodic reevaluations.

2) [Temazepam](#) 7.5 milligrams was safe and effective in the treatment of insomnia in 8 elderly subjects (mean age 67 years) with short-term use in a 14-day study [11]. Eight insomniac subjects were given placebo for 4 nights (baseline), [temazepam](#) for 7 nights, and placebo

for 3 nights (withdrawal). In the first 3 days of drug administration, there was significant improvement in total wake time and wake time after sleep onset compared to baseline. However, tolerance developed rapidly; during the final 3 nights of the study, sleep latency, total wake time, and wake time after sleep onset decreased but were not significantly different from baseline. Total wake time during the withdrawal period returned to baseline values. No major adverse effects were reported.

3) **Temazepam** 15 milligrams significantly decreased arousals and wake time during the night in 7 male patients with **congestive heart failure** who had insomnia secondary to Cheyne-Stokes respiration [12]. However, **temazepam** did not significantly improve sleep architecture. **Oxygen saturation** was not adversely affected by **temazepam**.

b) Shift-work/Jet-lag-related insomnia

1) **Temazepam** had no carry-over effect when used in the afternoon to induce sleep before a simulated night-shift [13]. Sleepiness was measured during the night after a daytime dose of **temazepam** 20 milligrams or placebo in 10 volunteers, to obtain a prophylactic sleep. **Temazepam** was more effective than placebo in maintaining diurnal sleep (320 minutes versus 214 minutes, p less than 0.02). This increased sleep time did not, however, cause any significant increase or decrease in sleepiness during the simulated night shift.

2) **Temazepam** was more efficacious than placebo in reducing the time to sleep onset and decreasing the number of awakenings in a double-blind, placebo-controlled, crossover trial. **Temazepam** 20 milligrams was administered to 10 healthy males the night prior to overseas travel and for 4 nights after arrival. No difference was found in duration of sleep, quality of sleep, dreaming, or state upon awakening. **Temazepam** did not adversely affect various performance measures, including reaction time, pencil and paper tests and logic tasks. Measurement of core body temperature, urinary 6-sulphatoxymelatonin, and urinary cortisol revealed that **temazepam** did not alter the rate of circadian rhythm adjustment to the new time zone [14].

c) Altitude insomnia

1) **Temazepam** improved sleep at high altitude in a study conducted at the base camp of Mount Everest at 5300 meters (Dubowitz et al, 1998). Men ($n=9$) and women ($n=2$) from the British Mount Everest Medical Expedition were randomly selected to receive **temazepam** 10 milligrams or placebo on their first night at base camp and then to receive the other agent on their second night. All reported improved sleep while receiving **temazepam** including quicker onset of sleep, better quality, fewer awakenings, and less awareness of periodic breathing. NO depressant effects were seen on the respiratory system with the mean **oxygen saturation** during sleep not being significantly changed with **temazepam**. Participants taking **temazepam** experienced fewer decreases in the number of times that saturation fell greater than 4% below the mean ($p=0.0036$).

2) **Temazepam** is effective for treating insomnia associated with high altitudes. Six subjects on an expedition in the Himalayas had their sleeping habits examined. At elevations between 4100 and 4846 meters, the subjects experienced altitude insomnia. **Temazepam** was concurrently administered with **acetazolamide** in 3 subjects being prophylactically treated for altitude sickness and in 3 subjects alone. In both cases, sleep latency was reduced by **temazepam**.

Temazepam combined with acetazolamide seems to enhance sleep as acetazolamide alone appears to sustain sleep at high altitudes [15].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Chlormezanone

4.6.A.1] Insomnia

a) Chlormezanone 400 milligrams and temazepam 20 milligrams were comparable in the treatment of 55 patients presenting with insomnia. Both treatment groups demonstrated an increase in the average duration of sleep and the frequency of waking refreshed; an improvement in the quality of sleep was also noted. No significant differences were noted between the treatment groups [214].

4.6.B] Clomethiazole

4.6.B.1] Insomnia

a) Temazepam and clomethiazole (chlormethiazole) were comparable in efficacy in the treatment of insomnia. Clomethiazole (chlormethiazole) 384 mg and temazepam 20 mg were compared in a double-blind, placebo controlled study involving 10 elderly (mean, 72.9 years) and 10 young (mean, 24.7 years) females. Both drugs shortened sleep latency and lengthened sleep time during the first half of the night. When awakened after 4 hours, the younger patients felt sedated after both drugs. The elderly patients felt as awake after the 2 drugs as they did after placebo. Clomethiazole (chlormethiazole) increased sleep duration during the second half of the night in the elderly, whereas both drugs increased sleep duration in the young. Both drugs are effective hypnotics and had no detectable pharmacologic action the next morning [192].

b) Temazepam is as effective as clomethiazole (chlormethiazole) for treating insomnia; however, temazepam may induce more daytime drowsiness than clomethiazole (chlormethiazole). Forty geriatric patients (aged 65 to 90 years) were administered temazepam 20 mg or clomethiazole (chlormethiazole) 384 mg for 6 nights each with 3-day placebo run-in and wash-out periods at the beginning of the study and between active agents. Both were effective for enhancing sleep quality and onset, but significantly more complaints of daytime drowsiness occurred with temazepam (Pathy et al, 1986).

c) Significant drowsiness and impaired performance with clomethiazole (chlormethiazole) was demonstrated in a single-dose study of temazepam 10 mg compared with clomethiazole (chlormethiazole) 384 mg in 9 elderly parkinsonian patients. All performance test scores returned to baseline within 6 hours however. Since it did not affect parkinsonian signs and symptoms or postural blood pressure, clomethiazole (chlormethiazole) was recommended as a safe and effective hypnotic in this patient population. The dose of temazepam used in this study did not produce sufficient hypnotic effects [193].

4.6.C] Clonidine

1) Efficacy

a) Clonidine was superior than TEMAZEPAM in decreasing the hypertensive response to PIN HEAD-HOLDER APPLICATION in patients undergoing CRANIOTOMY. Fifty patients were randomized to receive either clonidine 3 micrograms per kilogram (mcg/kg) or temazepam 10 or 20 milligrams orally 90 minutes before induction of anesthesia. Propofol was the main anesthetic agent. Mean arterial blood pressure (MAP) increased significantly in both groups after intubation and pin head-holder application (p less than 0.001). However MAP was significantly lower in the clonidine group after pin head-holder application (p =0.031 when compared with the temazepam group). Heart

rate and number of interventions to treat blood pressure were not significantly different between the groups (Costello et al, 1998).

4.6.D] Diazepam

4.6.D.1] Operation on mouth - Sedation

a) Oral [temazepam](#) is as effective as intravenous [diazepam](#) for sedation during oral surgery [213]. 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.E] Flunitrazepam

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

a) [Temazepam](#) was as effective for premedication the night prior to and the day of surgery as flunitrazepam. Forty patients were randomly divided into two equal groups and administered either [temazepam](#) 20 milligrams at bedtime and 20 milligrams the morning of the surgery or flunitrazepam 1 milligram in the same manner. Of various parameters measured, flunitrazepam was equivalent to [temazepam](#) except for prevention of cardiovascular changes and hormonal stress reaction. In these areas, flunitrazepam was considered superior to [temazepam](#) [212].

4.6.E.2] Insomnia

a) Flunitrazepam was more effective in treating insomnia than [temazepam](#). In a multicenter trial, 246 patients randomly received either flunitrazepam 1 milligram or [temazepam](#) 20 milligrams at bedtime for a minimum of 7 or a maximum of 14 nights. Flunitrazepam was significantly more effective for improving sleep onset and reducing awakenings [211].

4.6.F] Flurazepam

4.6.F.1] Insomnia

a) The efficacy and safety of [temazepam](#) 30 milligrams and [flurazepam](#) 30 milligrams were similar in a double-blind study of 75 geriatric patients with insomnia [196]. There was less drug hangover with [temazepam](#) than with [flurazepam](#) due to the shorter half-life of [temazepam](#). Also, [flurazepam](#) has a long-acting metabolite while [temazepam](#) has no active metabolites.

b) [Temazepam](#) was as effective as [flurazepam](#) for inducing sleep but did not cause performance problems the day after therapy. Twenty-four healthy subjects (12 men and 12 women) were administered [flurazepam](#) 30 milligrams, [temazepam](#) 40 milligrams, and then placebo. Subjectively, [flurazepam](#) induced more satisfactory sleep than [temazepam](#), but 3 mental function tests demonstrated [temazepam](#) caused less impairment than [flurazepam](#) [197].

c) Both [temazepam](#) and [triazolam](#) induced maximum sedative effects that corresponded to maximum plasma levels in a single-dose, placebo-controlled, double-blind study in 52 healthy subjects. [Triazolam](#) 0.25 mg induced greater sedation than [temazepam](#) 15 milligrams, but both agents were more sedative than [flurazepam](#) 15 milligrams. Recovery corresponded in all agents to elimination half-life, although sedative effects were abolished prior to plasma elimination. Sedative effects were greatest for [triazolam](#) followed by [temazepam](#), with [flurazepam](#) being similar to placebo [198].

4.6.G] Loprazolam

4.6.G.1] Insomnia

a) In a single-blind, randomized study of 197 patients with disturbed sleep patterns, lorazepam 1 milligram (mg) and **temazepam** 20 mg demonstrated similar hypnotic activity (improved ease in getting to sleep, improved depth of sleep, increased sleep duration, decreased awakenings at night). Each drug was statistically superior to placebo (p less than 0.01) and there were no statistical differences in adverse event profile (including drug-placebo comparison) [194].

4.6.H] Lorazepam**4.6.H.1] Anxiety**

a) All drugs were equally efficacious in relieving anxiety and depression in a study involving 51 psychiatric outpatients comparing **lorazepam** 2 milligrams with **temazepam** 20 milligrams and placebo. Lorazepam-treated patients had more side effects than placebo-treated patients [189].

4.6.H.2] Insomnia

a) **Lorazepam** 2 milligrams, **oxazepam** 30 milligrams, and **temazepam** 20 milligrams were equally efficacious in maintaining sleep in 20 psychogeriatric inpatients. Three patients experienced prolonged insomnia induced by the withdrawal of **lorazepam**. Lorazepam-treated patients had muscle relaxant effects after awakening [190].

b) **Temazepam** is as effective as **lorazepam** for treating sleep disturbance disorders. One hundred eighty-five patients randomly received **temazepam** 20 milligrams, **lorazepam** 1 milligrams, or placebo in a multicenter, single-blind study. Both active agents were significantly better than placebo for inducing sleep, but no difference was observed between **lorazepam** and **temazepam** [191].

4.6.I] Midazolam**4.6.I.1] Administration of medication - Preoperative care**

a) **Temazepam** is as effective as **midazolam** for sedation prior to surgical procedures. **Temazepam** 20 milligrams (mg) and **midazolam** 15 mg demonstrated equal efficacy and similar residual effects when administered orally as premedicants [210]; (Irjala et al, 1989); however, in one study, **midazolam** produced a greater incidence of drowsiness [210].

4.6.I.2] Insomnia

a) **Midazolam** 15 milligrams (mg) orally was significantly better than **temazepam** 30 mg orally for improving sleep latency in 175 patients with **chronic insomnia** who received active medication for a month. However, **temazepam** was significantly better in reducing early morning awakenings. Thirty-three patients chose to continue the study for an additional 2 months. Tolerance was not demonstrated in either group. In fact, total sleep time in the **midazolam** group was significantly higher at the end of 3 months than during the first week of treatment. Rebound insomnia was not noted. To the contrary, the **midazolam** group showed improved sleep latency and sleep time during the withdrawal period compared with baseline values [209].

4.6.J] Nitrazepam**4.6.J.1] Insomnia**

a) **Temazepam** in mean doses of 13.2 milligrams at bedtime was comparable to nitrazepam 5.2 milligrams at bedtime in maintaining quality and duration of sleep, patient satisfaction, depth of sleep, and reducing

number of awakenings. The hypnotic effects of [temazepam](#) and nitrazepam were compared in 31 psychiatric in-patients (19 to 76 years) in a double-blind study. Hangover effects were more significant in patients receiving [temazepam](#) [207].

4.6.J.2) Efficacy

a) Sedation induced by nitrazepam was observed to diminish with additional doses, but no tolerance was noted upon repeated doses of [temazepam](#). Eight healthy subjects were administered nitrazepam 10 milligrams, [temazepam](#) 20 milligrams, or placebo for 6 nights in a double-blind, randomized, crossover trial. Sedative effects were measured by saccadic eye movements, critical flicker fusion, choice reaction time, and subjective evaluations [208].

4.6.K] Opium

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

a) A double-blind controlled study comparing papaveretum (hydrochlorides of [opium alkaloids](#)) with oral [temazepam](#) showed more recall of the procedure of [bronchoscopy](#), a fall in mean arterial oxygen tension, and a higher rise in mean arterial carbon dioxide tension with papaveretum [203].

4.6.L] Oxazepam

4.6.L.1] Insomnia

a) [Lorazepam](#) 2 mg, [oxazepam](#) 30 milligrams, and [temazepam](#) 20 milligrams were effective in maintaining sleep although none reduced initial sleep latency in a double-blind study in 20 psychogeriatric inpatients [195]. Each drug was administered for 7 nights. Withdrawal insomnia occurred on the first night after [oxazepam](#) treatment was stopped, and to a lesser degree after [temazepam](#) treatment. Three patients experienced prolonged insomnia after [lorazepam](#) withdrawal. Both [lorazepam](#) and [oxazepam](#) had muscle relaxant side effects.

4.6.M] Quazepam

4.6.M.1] Insomnia

a) [Quazepam](#) 15 milligrams was significantly more effective in improving sleep than [temazepam](#) 15 milligrams, both with short-term and intermediate-term use in 22 nighttime laboratory sleep studies [206]. [Temazepam](#) was effective for short-term use but there was rapid development of tolerance with intermediate-term use. [Quazepam](#) was associated with significant daytime sleepiness. Upon withdrawal, [temazepam](#) was associated with some sleep and [mood disturbance](#), whereas [quazepam](#) had a more prolonged effectiveness.

4.6.N] Triazolam

1) Efficacy

a) Both [temazepam](#) and [triazolam](#) induced maximum sedative effects that corresponded to maximum plasma levels in a single-dose, placebo-controlled, double-blind study in 52 healthy subjects. [Triazolam](#) 0.25 milligram induced greater sedation than [temazepam](#) 15 milligrams, but both agents were more sedative than [flurazepam](#) 15 milligrams. Recovery corresponded in all agents to elimination half-life, although sedative effects were abolished prior to plasma elimination. Sedative effects were greatest for [triazolam](#) followed by [temazepam](#), with [flurazepam](#) being similar to placebo [204].

b)) In 2 small studies, [triazolam](#) impaired behavior more than [temazepam](#) [205]. In a comparative study of the behavioral effects of [temazepam](#) 15 to 30 milligrams versus [triazolam](#) 0.25 to 0.5 milligram, behavior was measured during 4-hour sessions with tests of immediate and delayed recall, learning, and psychomotor performance in 6 healthy male volunteers. A second experiment in 8 healthy male volunteers compared [triazolam](#) 0.5 mg to [temazepam](#) 60 mg, using the same battery of tests. In this case, [temazepam](#) disrupted behavior more than [triazolam](#). Studies are needed to elucidate precise dosage equivalence between these 2 hypnotics.

4.6.O] [Trimeprazine](#)

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

a) [Trimeprazine](#) was shown to produce significantly more preoperative sedation but also to prolong recovery time in a placebo-controlled comparison of [trimeprazine](#) 4 milligrams/kilogram to [temazepam](#) 1 milligram/kilogram in 85 children undergoing otolaryngological surgery. [Retrograde amnesia](#) occurred significantly more frequently in the [trimeprazine](#) group and vomiting was significantly less frequent [201].

b)) In a similar study, [trimeprazine](#) 3 milligrams/kilogram was comparable to [temazepam](#) 0.5, 1, and 1.5 milligrams/kilogram as premedication in 220 children undergoing elective surgery. No differences were noted in efficacy although [temazepam](#) was associated with a greater frequency of [ectopic beats](#) under [anesthesia](#) and more postoperative restlessness and vomiting [202].

4.6.P] [Zolpidem](#)

1) Efficacy

a)) Mean reaction time to collision, via car simulation, was not significantly different between women receiving one dose of [zolpidem](#), [temazepam](#), or placebo. In small double-blind, randomized, double-dummy, 3-session cross-over design study, 18 women (aged 35 to 58) received 10 mg [zolpidem](#), 20 mg [temazepam](#), and placebo at 2 am followed by a 3 to 14 day washout period. The primary endpoint was mean reaction time to collision in a car driving stimulation that occurred 7:30 am following drug administration. The mean time to collision was not statistically different between groups: baseline, 0.120 seconds (s), placebo: 0.124s, [temazepam](#): 0.118s, [zolpidem](#): 0.124; p greater than or equal to 0.12 for all pairwise comparisons. Lane position deviation was greater after administration of [zolpidem](#) compared to both placebo (p=0.025) and [temazepam](#) (p=0.05). The authors noted that two patients had a high number of collisions and patients taking hypnotics early in the morning, not drive later that morning (Parinen et al, 2003).

4.6.Q] [Zopiclone](#)

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

a) [Temazepam](#) was as effective as zopiclone for treating sleep disturbances. Sixty patients were administered zopiclone 7.5 milligrams and [temazepam](#) 20 milligrams for 3 weeks in a double-blind, crossover, placebo-controlled study. Both agents were equally effective, and were significantly more effective than placebo [199].

4.6.Q.2) Efficacy

a) Zopiclone 7.5 milligrams was as effective as [temazepam](#) 20 milligrams in facilitating sleep in patients the night before surgery [200]. Sixty patients were administered either zopiclone, [temazepam](#), or placebo in a double blind, randomized, placebo-controlled study. Subjective measurements of quality of sleep

and objective measurements of residual impairment indicated that both [temazepam](#) and zopiclone were equally effective and significantly more effective than placebo. Both agents had similar residual effects.

6.0] References

- 1 Siciliani O, Schiavon M, & Tansella M: Anxiety and EEG alpha activity in neurotic patients: baseline correlations and changes during a double-blind trial with temazepam. *Acta Psychiatr Scand* 1975; 52:116-131.
- 2 Cesa-Bianchi M, Ghirardi P, & Ravaccia F: A preliminary double-blind study with SB 5833 (camazepam), a new benzodiazepine derivative. *Arzneimittelforschung* 1974; 24:2032-2035.
- 3 Sarteschi P, Cassano GB, Castrogiovanni P, et al: Major and minor tranquilizers in the treatment of anxiety states. *Arzneimittelforschung* 1972; 22:93-97.
- 4 Product Information: RESTORIL(R) oral capsules, temazepam oral capsules. Mallinckrodt, St. Louis, MO, 2002.
- 5 Cuanang JR & Limos L: Treatment of insomnia with temazepam: double-blind, placebo-controlled evaluation. *Clin Ther* 1982; 4:402-412.
- 6 Okuma T, Matsuoka H, Matsue Y, et al: Model insomnia by methylphenidate and caffeine and use in the evaluation of temazepam. *Psychopharmacology* 1982; 76:201-208.
- 7 Heffron WA & Roth P: Double-blind evaluation of the safety and hypnotic efficacy of temazepam in insomniac outpatients. *Br J Clin Pharmacol* 1979; 8:69S-72S.
- 8 Bixler EO, Kales A, Soldatos CR, et al: Effectiveness and temazepam with short-, intermediate- and long-term use. *J Clin Pharmacol* 1978; 18:110-118.
- 9 Harry TVA & Johnson PA: The effectiveness of temazepam as an hypnotic: an open, multicentre assessment in 804 patient with sleep disorders. *Curr Med Res Opin* 1978; 5:476-483.
- 10 Clarke CH & Nicholson AN: Immediate and residual effects in man of the metabolites of diazepam. *Br J Clin Pharmacol* 1978; 6:325-331.
- 11 Vgontzas AM, Kales A, Bixler EO, et al: Temazepam 7.5 mg: effects on sleep in elderly insomniacs. *Eur J Clin Pharmacol* 1994; 46:209-213.
- 12 Biberdorf DJ, Steens R, Millar TW, et al: Benzodiazepines in congestive heart failure: effects of temazepam on arousability and Cheyne-Stokes respiration. *Sleep* 1993; 16:529-538.
- 13 Porcu S, Bellatreccia A, Ferrara M, et al: Acutely shifting the sleep-wake cycle: nighttime sleepiness after diurnal administration of temazepam or placebo. *Aviat Space Environ Med* 1997; 68:688-694.
- 14 Donaldson E & Kennaway DJ: Effects of temazepam on sleep, performance, and rhythmic 6-sulphatoxymelatonin and cortisol excretion after transmeridian travel. *Aviat Space Environ Med* 1991; 62:654-660.
- 15 Nicholson AN, Smith PA, Stone BM, et al: Effects of acetazolamide and temazepam on sleep at high altitude (abstract). *Postgrad Med J* 1987; 63:191-193.
- 16 O'Callaghan C, Milner AD, & Swarbrick A: Problems encountered using temazepam syrup for sedation in infants. *Eur J Pediatr* 1988; 147:523-524.
- 17 Ochs HR, Greenblatt DJ, Verburg-Ochs B, et al: Temazepam clearance unaltered in cirrhosis. *Am J Gastroenterol* 1986; 81:80-84.
- 18 Ghabrial H, Desmond PV, Watson KJR, et al: The effects of age and chronic liver disease on the elimination of temazepam. *Eur J Clin Pharmacol* 1986; 30:93-97.

- 19 Bass NM & Williams RL: Guide to drug dosage in hepatic disease. *Clin Pharmacokinet* 1988; 15:396-420.
- 20 Bakti G, Fisch HU, Karlaganis G, et al: Mechanism of the excessive sedative response of cirrhotics to benzodiazepines: model experiments with triazolam. *Hepatology* 1987; 7:629-638.
- 21 Andreasen PB, Hendel J, Greisen G, et al: Pharmacokinetics of diazepam in disordered liver function. *Eur J Clin Pharmacol* 1976; 10:115-120.
- 22 Shull HJ, Wilkinson GR, Johnson R, et al: Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; 84:420.
- 23 Greenblatt DJ & Shader RI: Drug therapy: benzodiazepines. *N Engl J Med* 1974; 291:1011.
- 24 US Food and Drug Administration: FDA Requests Label Change for All Sleep Disorder Drug Products. US Food and Drug Administration. Rockville, MD. 2007. Available from URL: <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01587.html>.
- 25 Product Information: RESTORIL(TM) oral capsules, temazepam oral capsules. Mallinckrodt Inc, Hazelwood, MO, 2008.
- 26 Ford GA, Hoffman BB, & Blaschke TF: Effect of temazepam on blood pressure regulation in healthy elderly subjects. *Br J Clin Pharmacol* 1990; 29:61-67.
- 27 Hudson MMT, Edmonds M, & Watkins PJ: Misuse of temazepam (letter). *Br Med J* 1991; 303:993.
- 28 Blair SA, Holcombe C, Coombes EN, et al: Leg ischaemia secondary to non-medical injection of temazepam (letter). *Lancet* 1991; 338:1393-1394.
- 29 Kales A, Manfredi RL, Vgontzas AN, et al: Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. *Clin Pharmacol Ther* 1991; 49:468-476.
- 30 Pleuvry BJ, Maddison SE, Odeh RB, et al: Respiratory and psychological effects of oral temazepam in volunteers. *Br J Anaesth* 1980; 52:901-906.
- 31 Hindmarch I, Parrott AC, Hickey BJ, et al: An investigation into the effects of repeated doses of temazepam on aspects of sleep, early morning behavior and psychomotor performance in normal subjects. *Drugs Exper Clin Res* 1980; 6:399-406.
- 32 Bailie R, Christmas L, Price N, et al: Effects of temazepam premedication on cognitive recovery following Alfentanil-propofol Anaesthesia. *Br J Anaesth* 1989; 63:68-75.
- 33 Janssen FH, Beecher L, Griep AC, et al: Short-term effects of temazepam in the EEGs of healthy volunteers. *Neuropsychobiology* 1989; 22:72-76.
- 34 Fisman M: Musical hallucinations: report of two unusual cases. *Can J psychiatry* 1991; 36:609-610.
- 35 Drake J: Temazepam 'planpak': a multicentre general practice trial in planned benzodiazepine hypnotic withdrawal. *Curr Med Res Opin* 1991; 12:390-393.
- 36 Conell LJ & Berlin RM: Withdrawal after substitution of a short-acting for a long-acting benzodiazepine. *JAMA* 1983; 250:2838-2839.
- 37 Ratna L: Addiction to temazepam. *Br Med J* 1981; 282:1837-1838.
- 38 Product Information: LUSEDRA(R) IV injection, fospropofol disodium IV injection. Eisai Corporation, Research Triangle Park, NC, 2008.
- 39 Product Information: Xyrem(R), sodium oxyburate oral solution. Orphan Medical, Inc., Minnetonka, MN, 2002.
- 40 Henauer SA, Hollister LE, Gillespie HK, et al: Theophylline antagonizes diazepam-induced psychomotor impairment. *Eur J Clin Pharmacol* 1983; 25:743-747.

- 41 Arvidsson S, Niemand D, Martinell S, et al: Aminophylline reversal of diazepam sedation. *Anaesthesia* 1984; 39:806-809.
- 42 Stirt JA: Aminophylline is a diazepam antagonist. *Anesth Analg* 1981; 60:767-768.
- 43 Meyer BH, Weis OF, & Muller FO: Antagonism of diazepam by aminophylline in healthy volunteers. *Anesth Analg* 1984; 63:900-902.
- 44 Wangler MA & Kilpatrick DS: Aminophylline is an antagonist of lorazepam. *Anesth Analg* 1985; 64:834-836.
- 45 Gallen JS: Aminophylline reversal of midazolam sedation (letter). *Anesth Analg* 1989; 69:268.
- 46 Gurel A, Elevli M, & Hamulu A: Aminophylline reversal of flunitrazepam sedation. *Anesth Analg* 1987; 66:333-336.
- 47 Sleight JW: Failure of aminophylline to antagonize midazolam sedation (letter). *Anesth Analg* 1986; 65:540.
- 48 Tuncok Y, Akpinar O, Guven H, et al: The effects of theophylline on serum alprazolam levels. *Int J Clin Pharmacol Ther* 1994; 32:642-645.
- 49 Stirt JA: Aminophylline is a diazepam antagonist. *Anesth Analg* 1981; 60:767-768.
- 50 Wangler MA & Kilpatrick DS: Aminophylline is an antagonist of lorazepam. *Anesth Analg* 1985; 64:834-836.
- 51 Gurel A, Elevli M, & Hamulu A: Aminophylline reversal of flunitrazepam sedation. *Anesth Analg* 1987; 66:333-336.
- 52 Gallen JS: Aminophylline reversal of midazolam sedation (letter). *Anesth Analg* 1989; 69:268.
- 53 Bonfiglio MF & Dasta JF: Clinical significance of the benzodiazepine-theophylline interaction. *Pharmacotherapy* 1991; 11:85-87.
- 54 Product Information: ROMAZICON(R) injection, flumazenil injection. Roche Laboratories, Inc, Nutley, NJ, 2007.
- 55 Kawaguchi A, Ohmori M, Tsuruoka S, et al: Drug interaction between St John's Wort and quazepam. *Br J Clin Pharmacol* 2004; 58(4):403-410. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 56 Dresser GK, Schwarz UI, Wilkinson GR, et al: Coordinate induction of both cytochrome P4503A and MDR1 by St John's wort in healthy subjects. *Clin Pharmacol Ther* 2003; 73(1):41-50.
- 57 Wang Z, Gorski JC, Hamman MA, et al: The effects of St. John's Wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 2001; 70(4):317-326.
- 58 Markowitz JS, Donovan JL, DeVane CL, et al: Effect of St John's Wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003; 290(11):1500-1504.
- 59 Gurley BJ, Gardner SF, Hubbard MA, et al: Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. *Clin Pharmacol Ther* 2002; 72(3):276-287.
- 60 Product Information: DOLOPHINE(R) oral tablets, methadone HCl oral tablets. Roxane Laboratories, Inc. (per FDA), Columbus, OH, 2014.
- 61 Abernethy DR, Greenblatt DJ, Steel K, et al: Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; 97:223-224.
- 62 Abernethy DR, Greenblatt DJ, Steel K, et al: Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; 97:223-224.
- 63 Product Information: Demerol(R), meperidine hydrochloride. Sanofi-Synthelabo Inc., New York, NY, 2002.
- 64 Product Information: Versed(R), midazolam HCl injection. Roche Pharmaceuticals, Nutley, NJ, 2000.

- 65 Product Information: BUNAVAIL(TM) buccal film, buprenorphine naloxone buccal film. BioDelivery Sciences International (per FDA), Raleigh, North Carolina, 2014.
- 66 Product Information: REMERONSolTab(R) oral disintegrating tablets, mirtazapine oral disintegrating tablets. Merck Sharp & Dohme Corp. (per FDA), Whitehouse Station, NJ, 2014.
- 67 Birket-Smith E & Mikkelsen B: Preliminary observations on the effect of a new benzodiazepine (RO-5-4023) in epilepsy. *Acta Neurol Scand* 1972; 48(suppl):385-395.
- 68 Aarli J: Effect of clonazepam (RO5-4023) on epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):11.
- 69 Mikkelsen B & Birket-Smith E: A clinical study of the benzodiazepine RO5-4023 (clonazepam) in the treatment of epilepsy. *Acta Neurol Scand* 1973; 49(suppl 53):91-96.
- 70 Munthe-Kaas A: Clonazepam in the treatment of epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):97.
- 71 Hooshmond H: Trial of a new anticonvulsant for uncontrollable minor motor seizures. *Epilepsia* 1971; 12:277.
- 72 Tverskoy M, Fleyshman G, Bradley EL, et al: Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg* 1988; 67:342-345.
- 73 Short TG, Galletly DC, & Plummer JL: Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; 66:13-19.
- 74 Product Information: Versed(R), midazolam. Roche Laboratories Inc., Nutley, NJ, 2000.
- 75 Wilder-Smith OHG, Ravussin PA, Decosterd LA, et al: Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1999; 83:590-595.
- 76 Birket-Smith E & Mikkelsen B: Preliminary observations on the effect of a new benzodiazepine (RO-5-4023) in epilepsy. *Acta Neurol Scand* 1972; 48(suppl):385-395.
- 77 Aarli J: Effect of clonazepam (RO5-4023) on epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):11.
- 78 Mikkelsen B & Birket-Smith E: A clinical study of the benzodiazepine RO5-4023 (clonazepam) in the treatment of epilepsy. *Acta Neurol Scand* 1973; 49(suppl 53):91-96.
- 79 Munthe-Kaas A: Clonazepam in the treatment of epileptic seizures. *Acta Neurol Scand* 1973; 49(suppl 53):97.
- 80 Hooshmond H: Trial of a new anticonvulsant for uncontrollable minor motor seizures. *Epilepsia* 1971; 12:277.
- 81 Product Information: BELSOMRA(R) oral tablets, suvorexant oral tablets. Merck Sharp & Dohme Corp. (per manufacturer), Whitehouse Station, NJ, 2014.
- 82 Carrasco MC, Vallejo JR, Pardo-de-Santayana M, et al: Interactions of *Valeriana officinalis* L. and *Passiflora incarnata* L. in a patient treated with lorazepam. *Phytother Res* 2009; 23(12):1795-1796. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 83 Holzl J & Godau P: Receptor binding studies with *Valeriana officinalis* on the benzodiazepine receptor. *Planta Med* 1989; 55:642.
- 84 Cavadas C, Araujo I, Cotrim MD, et al: In vitro study on the interaction of *Valeriana officinalis* L. extracts and their amino acids on GABA-A receptor in rat brain. *Arzneim-Forsch/Drug Res* 1995; 45(7):753-755.
- 85 Santos MS, Ferreira F, Faro C, et al: The amount of GABA present in aqueous extracts of valerian is sufficient to account for (3H)GABA release in synaptosomes. *Planta Med* 1994; 60(5):475-476.
- 86 Holzl J & Godau P: Receptor binding studies with *Valeriana officinalis* on the benzodiazepine receptor. *Planta Med* 1989; 55:642.

- 87 Kriegelstein VJ & Grusla D: Central dampfende Inhaltsstoffe im Baldrian: Valepotriate, Valeransäure, Valeranon und atherisches Öl sind jedoch unwirksam. *Deutsche Apotheker Zeitung* 1988; 40:2041-2046.
- 88 Medina JH, Pena C, deStein ML, et al: Benzodiazepine-like molecules, as well as other ligands for the brain benzodiazepine receptors are relatively common constituents of plants. *Biochem Biophys Res Comm* 1989; 165:547-553.
- 89 Mennini T, Bernasconi P, Bombardelli F, et al: In vitro study on the interaction of extracts and pure compounds from *Valeriana officinalis* roots with GABA, benzodiazepine and barbiturate receptors in rat brain. *Fitoterapia* 1993; 64:291-300.
- 90 Mennini T, Bernasconi P, Bombardelli F, et al: In vitro study on the interaction of extracts and pure compounds from *Valeriana officinalis* roots with GABA, benzodiazepine and barbiturate receptors in rat brain. *Fitoterapia* 1993; 64:291-300.
- 91 Product Information: GATTEX(R) subcutaneous injection powder, teduglutide (rDNA origin) subcutaneous injection powder. Hospira, Inc. (per manufacturer), McPherson, KS, 2012.
- 92 Almeida JC & Grimsley EW: Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; 125:940-941.
- 93 Almeida JC & Grimsley EW: Coma from the health food store: interaction between kava and alprazolam (letter). *Ann Intern Med* 1996; 125:940-941.
- 94 Jussofie, SA, & Hiemke C: Kavapyrone enriched extract from *Piper methysticum* as modulator of the GABA binding site in different regions of rat brain. *Psychopharmacology (Berl)* 1994; 116:469-474.
- 95 Kuribara H, Stavinocha WB, & Maruyama Y: Behavioral pharmacological characteristics of honokiol, an anxiolytic agent present in extracts of magnolia bark, evaluated by an elevated plus-maze test in mice. *J Pharm Pharmacol* 1998; 50:819-826.
- 96 Tsai TH, Chou CJ, Cheng FC, et al: Pharmacokinetics of honokiol after intravenous administration in rats assessed using high-performance liquid chromatography. *J Chromatograph* 1994; 655(1):41-45.
- 97 Watanabe H, Watanabe K, & Hagino K: Chemostructural requirement for centrally acting muscle relaxant effect of magnolol and honokiol, neolignane derivatives. *J Pharm Dyn* 1983a; 6:184-190.
- 98 Watanabe K, Watanabe H, Goto Y, et al: Pharmacological properties of magnolol and honokiol extracted from *Magnolia officinalis*: central depressant effects. *Planta Med* 1983b; 49:103-108.
- 99 Watanabe H, Watanabe K, Goto Y, et al: Studies on the principles of *Magnolia* bark. Centrally acting muscle relaxant activity of magnolol and honokiol. *Jpn J Pharmacol* 1975; 25:605-607.
- 100 Watanabe H, Watanabe K, & Hagino K: Chemostructural requirement for centrally acting muscle relaxant effect of magnolol and honokiol, neolignane derivatives. *J Pharm Dyn* 1983a; 6:184-190.
- 101 Watanabe K, Watanabe H, Goto Y, et al: Pharmacological properties of magnolol and honokiol extracted from *Magnolia officinalis*: central depressant effects. *Planta Med* 1983b; 49:103-108.
- 102 Watanabe H, Watanabe K, Goto Y, et al: Studies on the principles of *Magnolia* bark. Centrally acting muscle relaxant activity of magnolol and honokiol. *Jpn J Pharmacol* 1975; 25:605-607.
- 103 Tsai TH, Chou CJ, Cheng FC, et al: Pharmacokinetics of honokiol after intravenous administration in rats assessed using high-performance liquid chromatography. *J Chromatograph* 1994; 655(1):41-45.
- 104 Kuribara H, Stavinocha WB, & Maruyama Y: Behavioral pharmacological characteristics of honokiol, an anxiolytic agent present in extracts of magnolia bark, evaluated by an elevated plus-maze test in mice. *J Pharm Pharmacol* 1998; 50:819-826.
- 105 Product Information: Karbinal(TM) ER oral extended-release suspension, carbinoxamine maleate oral extended-release suspension. Tris Pharma (per FDA), Monmouth Junction, NJ, 2013.

- 106 Product Information: carbinoxamine maleate oral tablets, oral syrup, carbinoxamine maleate oral tablets, oral syrup. Breckenridge Pharmaceutical, Inc. (per DailyMed), Boca Raton, FL, 2012.
- 107 Medina JH, Paladini RC, Wolfman C, et al: Chrysin (5,7-di-OH-flavone), a naturally-occurring ligand for benzodiazepine receptors with anticonvulsant properties. *Biochem Pharmacol* 1990; 40(10):2227-2231.
- 108 Speroni E, Billi R, Crespi Perellino N, et al: Role of chrysin in the sedative effects of *Passiflora incarnata* L. *Phytother Res* 1996; 10:S98-S100.
- 109 Gattuso S, Di Sapio O, McCargo J, et al: *Passiflora caerulea* (sic) and its adulterator *Cucurbitella asperata*. *Fitoterapia* 1996; 67(6):535-544.
- 110 Product Information: OxyContin(R) oral controlled-release tablets, oxycodone HCl oral controlled-release tablets. Purdue Pharma L.P. (per FDA), Stamford, CT, 2013.
- 111 Product Information: XARTEMIS(TM) XR oral extended-release tablets, oxycodone hydrochloride acetaminophen oral extended-release tablets. Mallinckrodt LLC (per manufacturer), Hazelwood, MO, 2014.
- 112 Lee CM, Wong HCN, Chui KY, et al: Miltirone, a central benzodiazepine receptor partial agonist from a Chinese medicinal herb *Salvia miltiorrhiza*. *Neurosci Lett* 1991; 127:237-41.
- 113 Lee CM, Wong HCN, Chui KY, et al: Miltirone, a central benzodiazepine receptor partial agonist from a Chinese medicinal herb *Salvia miltiorrhiza*. *Neurosci Lett* 1991; 127:237-41.
- 114 Product Information: ANTIVERT(R) oral tablets, meclizine HCl oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 115 Product Information: ANTIVERT(R)/25 oral tablets, meclizine HCl 25mg oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 116 Product Information: ANTIVERT(R)/50 oral tablets, meclizine HCl 50mg oral tablets. Pfizer Inc. (per FDA), New York, NY, 2012.
- 117 Product Information: NUCYNTA(TM) immediate-release oral tablets, tapentadol immediate-release oral tablets. PriCara, Raritan, NJ, 2009.
- 118 Product Information: DURAGESIC(R) transdermal system, fentanyl transdermal system. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2012.
- 119 Product Information: ADASUVE(TM) oral inhalation powder, loxapine oral inhalation powder. Alexza Pharmaceuticals, Inc. (per manufacturer), Mountain View, CA, 2012.
- 120 Product Information: loxapine oral capsules, loxapine oral capsules. Lannett Company, Inc. (per DailyMed), Philadelphia, PA, 2011.
- 121 Hobbs W, Rall T, & Verdoorn T: Hypnotic sedatives - ethanol In: Hardman J & Limbird L (Eds): *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th. McGraw-Hill, New York, NY, 1996, pp 361-396.
- 122 Ishihara K, Kushida J, Yuzurihara M, et al: Interaction of drugs and Chinese herbs: pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J Pharm Pharmacol* 2000; 52(8):1023-1029.
- 123 Ishihara K, Kushida J, Yuzurihara M, et al: Interaction of drugs and Chinese herbs: pharmacokinetic changes of tolbutamide and diazepam caused by extract of *Angelica dahurica*. *J Pharm Pharmacol* 2000; 52(8):1023-1029.
- 124 Hui KM, Wang XH, & Xue H: Interaction of flavones from the roots of *Scutellaria baicalensis* with the benzodiazepine site. *Planta Med* 2000; 66(1):91-93.
- 125 Liao JF, Wang HH, Chen MC, et al: Benzodiazepine binding site-interactive flavones from *Scutellaria baicalensis* root. *Planta Med* 1998; 64(6):571-572.

- 126 Hui KM, Wang XH, & Xue H: Interaction of flavones from the roots of *Scutellaria baicalensis* with the benzodiazepine site. *Planta Med* 2000; 66(1):91-93.
- 127 Liao JF, Wang HH, Chen MC, et al: Benzodiazepine binding site-interactive flavones from *Scutellaria baicalensis* root. *Planta Med* 1998; 64(6):571-572.
- 128 Parfitt K (ed): *Martindale: The Complete Drug Reference*. London: Pharmaceutical Press (Electronic version). Micromedex, Inc., Greenwood Village, CO, Edition expires 09/2002.
- 129 Product Information: Parafon Forte DSC(R), chlorzoxazone tablets. Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, 2000.
- 130 Product Information: Dantrium(R), dantrolene sodium capsules. Procter and Gamble Pharmaceuticals, Cincinnati, OH, 1997.
- 131 Product Information: Soma(R), carisporodol tablets. Wallace Laboratories, Cranbury, NJ, 1994.
- 132 Product Information: FYCOMPA(TM) oral tablets, perampanel oral tablets. Eisai Inc. (per Manufacturer), Woodcliff Lake, NJ, 2012.
- 133 Product Information: YAZ(R) oral tablets, drospirenone, ethinyl estradiol oral tablets. Berlex, Inc, Montville, NJ, 2006.
- 134 Stoehr GP, Kroboth PD, Juhl RP, et al: Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; 36:683-690.
- 135 Stoehr GP, Kroboth PD, Juhl RP, et al: Effect of oral contraceptives on triazolam, temazepam, alprazolam, and lorazepam kinetics. *Clin Pharmacol Ther* 1984; 36:683-690.
- 136 Product Information: Placidyl(R), ethchlorvynol capsules. Abbott Laboratories, Abbott Park, IL, 1994.
- 137 Product Information: Zohydro(TM) ER oral extended-release capsules, hydrocodone bitartrate oral extended-release capsules. Zogenix, Inc. (per FDA), Emeryville, CA, 2013.
- 138 Product Information: AMBIEN(R) oral tablets, zolpidem tartrate oral tablets. Sanofi-Aventis US, LLC, Bridgewater, NJ, 2008.
- 139 Product Information: Priftin(R), rifapentine. Aventis Pharmaceuticals, Inc., Kansas City, MO, 2000.
- 140 Kunsman GW, Manno JE, Przekop MA, et al: The effects of temazepam and ethanol on human psychomotor performance. *Eur J Clin Pharmacol* 1992; 43:603-611.
- 141 Kunsman GW, Manno JE, Przekop MA, et al: The effects of temazepam and ethanol on human psychomotor performance. *Eur J Clin Pharmacol* 1992; 43:603-611.
- 142 File SE, Bond AJ, & Lister RG: Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* 1982; 2:102-106.
- 143 File SE, Bond AJ, & Lister RG: Interaction between effects of caffeine and lorazepam in performance tests and self-ratings. *J Clin Psychopharmacol* 1982; 2:102-106.
- 144 Mattila MJ & Nuotto E: Caffeine and theophylline counteract diazepam effects in man. *Med Biol* 1983; 61:337-343.
- 145 Mattila MJ, Palva E, & Savolainen K: Caffeine antagonizes diazepam effects in man. *Med Biol* 1982; 60:121-123.
- 146 Product Information: Restoril(R), temazepam. Mallinckrodt Inc, St Louis, MO, 2002.
- 147 Therapeutic Goods Administration: Prescribing medicines in pregnancy database. Therapeutic Goods Administration. Woden, Australian Capital Territory, Australia. 2011. Available from URL: <http://www.tga.gov.au/hp/medicines-pregnancy.htm>. As accessed 2011-06-20.

- 148 Laegried L: Neurodevelopment in late infancy after prenatal exposure to benzodiazepines-- a prospective study. *Neuropediatrics* 1992; 23:60-67.
- 149 Laegreid L, Olegard R, Walstrom J, et al: Teratogenic effects of benzodiazepine use during pregnancy. *J Pediatr* 1989; 114:126-131.
- 150 Restrepo M, Munoz M, Day N, et al: Birth defects among children born to a population occupationally exposed to pesticides in Colombia. *Scand J work Environ Health* 1990; 16:239-246.
- 151 Bracken MG & Holford TR: Exposure to prescribed drugs in pregnancy and association with congenital malformations. *Obstet Gynecol* 1981; 58:336-345.
- 152 Rothman KJ, Fyler DC, Golblatt A, et al: Exogenous hormones and other drug exposures of children with congenital heart disease. *Am J Epidemiol* 1979; 109:433-439.
- 153 Tikkanen J & Heinonen OP: Risk factors for ventricular septal defect in Finland. *Public Health* 1991; 105:99-112.
- 154 Czeizel A: Lack of evidence of teratogenicity of benzodiazepine drugs in Hungary. *Reprod Toxicol* 1988; 1:183-188.
- 155 Aseleton P, Jick H, Milunsky A, et al: First-trimester drug use and congenital disorders. *Obstet Gynecol* 1985; 65:451-455.
- 156 Zierler S & Rothman KJ: Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. *N Engl J Med* 1985; 313:347-352.
- 157 Gidai J, Acs N, Banhid F, et al: Congenital abnormalities in children of 43 pregnant women who attempted suicide with large doses of nitrazepam. *Pharmacoepidemiol Drug Saf* 2010; 19(2):175-182. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 158 Dolovich LR, Addis A, Regis JM, et al: Benzodiazepine use in pregnancy and major malformations or oral cleft: Meta-analysis of cohort and case-control studies. *BMJ* 1998; 317(7162):839-843.
- 159 Kargas GA & Kargas SA: Perinatal mortality due to interaction of diphenhydramine and temazepam. *N Engl J Med* 1985; 313:1417.
- 160 Rementeria JL & Bhatt K: Withdrawal symptoms in neonates from intrauterine exposure to diazepam. *J Pediatr* 1977; 90:123-126.
- 161 Laegreid L, Olegard R, Walstrom J, et al: Teratogenic effects of benzodiazepine use during pregnancy. *J Pediatr* 1989; 114:126-131.
- 162 Iqbal MM, Sobhan T, & Ryals T: Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatric Services* 2002; 53(1):39-49.
- 163 Product Information: Sonata(R), zaleplon capsules. Wyeth Laboratories, Philadelphia, PA, 2003.
- 164 Product Information: Ambien(R), zolpidem tartrate. Sanofi-Synthelabo Inc., New York, NY, 2002.
- 165 Anon: American academy of pediatrics committee on drugs: transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108(3):776-789.
- 166 Lebedevs TH, Wojnar-Horton RE, Yapp P, et al: Excretion of temazepam in breast milk (letter). *Br J Clin Pharmacol* 1992; 33:204-206.
- 167 Anon: Breastfeeding and Maternal Medication. World Health Organization, Geneva, Switzerland, 2002.
- 168 Kupfer DJ & Reynolds CF: Management of insomnia. *N Engl J Med* 1997; 336(5):341-346. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 169 Ratcliff A, Indalo AA, Bradshaw EG, et al: Premedication with temazepam in minor surgery. *Anaesthesia* 1989; 44:812-815.

- 170 Fuccella LM, Tosolini G, Moro E, et al: Study of physiological availability of temazepam in man. *Int J Clin Pharmacol Ther Toxicol* 1972; 6:303-309.
- 171 Ochs HR, Greenblatt DJ, & Heuer H: Is temazepam an accumulating hypnotic?. *J Clin Pharmacol* 1984; 24:58-64.
- 172 Product Information: Restoril(R), temazepam. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 1999.
- 173 Divoll M, Greenblatt DJ, Harmatz JS, et al: Effect of age and gender on disposition of temazepam. *J Pharm Sci* 1981; 70:1104-1107.
- 174 Badcock NR, Osborne GA, Nyman TLM, et al: Plasma and cerebrospinal fluid concentrations of temazepam following oral drug administration. *Eur J Clin Pharmacol* 1990; 38:153-155.
- 175 Schwarz HJ: Pharmacokinetics and metabolism of temazepam in man and several animal species. *Br J Clin Pharmacol* 1979; 8:23S-29S.
- 176 Fuccella LM, Bolcioni G, Tamassia G, et al: Human pharmacokinetics and bioavailability of temazepam administered in soft gelatin capsules. *Eur J Clin Pharmacol* 1977; 12:383-386.
- 177 Gilman AG, Goodman LS, & Gilman AGilman AG, Goodman LS, & Gilman A (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th. Macmillan Publishing Co, New York, NY, 1980.
- 178 Mao CC, Marco E, Revuelta A, et al: The turnover rate of gamma-aminobutyric acid in the nuclei of telencephalon: implications in the pharmacology of antipsychotics and of a minor tranquilizer. *Biol Psychiatry* 1977; 12:359-371.
- 179 Squires RF & Braestrup C: Benzodiazepine receptors in rat brain. *Nature* 1977; 266:732-734.
- 180 Schallek W, Horst WD, & Schlosser WSchallek W, Horst WD, & Schlosser W: Mechanisms of Action of Benzodiazepines, In: *Advances in Pharmacology and Chemotherapy*, Academic Press, New York, 1979.
- 181 Haefely W: Synaptic pharmacology of barbiturates and benzodiazepines. *Agents Actions Suppl* 1977; 7:353-359.
- 182 Harry TVA & Latham AN: Hypnotic and residual effects of temazepam in volunteers (letter). *Br J Clin Pharmacol* 1980; 9:618-620.
- 183 Heel RC, Brogden RN, Speight TM, et al: Temazepam: a review of its pharmacological properties and therapeutic efficacy as an hypnotic. *Drugs* 1981; 21:321-340.
- 184 Lader MH: Insomnia and short-acting benzodiazepine hypnotics. *J Clin Psychiatry* 1983; 44:47-53.
- 185 Kales A & Kales JD: Sleep laboratory studies of hypnotic drugs: efficacy and withdrawal effects. *J Clin Psychopharmacol* 1983; 3:140-150.
- 186 Rickels K: Clinical trials of hypnotics. *J Clin Psychopharmacol* 1983; 3:133-139.
- 187 Nicholson AN: Hypnotics: their place in therapeutics. *Drugs* 1986; 31:164-176.
- 188 Product Information: Restoril(R), temazepam. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 1999.
- 189 Ihalainen O, Viukari M, Jaaskelainen J, et al: Lorazepam, temazepam, placebo and assessment visits in psychiatric out-patients with anxiety. *Pharmatherapeutica* 1981; 2:628-636.
- 190 Linnoila M, Viukari M, Lamminsivu U, et al: Efficacy and side effects of lorazepam, oxazepam, and temazepam as sleeping aids in psychogeriatric inpatients. *Int Pharmacopsychiatr* 1980; 15:129-135.
- 191 Gringras M, Beaumont G, & Ankier SI: A comparison of the hypnotic activity of loperazolam, temazepam and placebo in general practice. *J Int Med Res* 1984; 12:10-16.

- 192 Briggs RS, Castleden CM, & Kraft CA: Improved hypnotic treatment using chlormethiazole and temazepam. *Br Med J* 1980; 280:601-604.
- 193 Tulloch JA, Ashwood TJ, Bateman DN, et al: A single-dose study of the pharmacodynamic effects of chlormethiazole, temazepam and placebo in elderly Parkinsonian patients. *Age Ageing* 1991; 20:424-429.
- 194 Gringras M, Beaumont G, & Ankier SI: A comparison of the hypnotic activity of lorazepam, temazepam and placebo in general practice. *J Int Med Res* 1984; 12:10-16.
- 195 Linnoila M, Viukari M, Lamminsivu U, et al: Efficacy and side effects of lorazepam, oxazepam, and temazepam as sleeping aids in psychogeriatric inpatients. *Int Pharmacopsychiatr* 1980; 15:129-135.
- 196 Fillingim JM: Double-blind evaluation of temazepam, flurazepam, and placebo in geriatric insomniacs. *Clin Ther* 1982; 4:369-380.
- 197 Wesnes K & Warburton DM: A comparison of temazepam and flurazepam in terms of sleep quality and residual changes in performance. *Neuropsychobiology* 1984; 11:255-259.
- 198 Greenblatt DJ, Harmatz JS, Engelhardt N, et al: Pharmacokinetic determinants of dynamic differences among three benzodiazepine hypnotics. *Arch Gen Psychiatry* 1989; 46:326-332.
- 199 van der Kleijn E: Effects of zopiclone and temazepam on sleep, behaviour and mood during the day. *Eur J Clin Pharmacol* 1989; 36:247-251.
- 200 Whitehead C, Sander L, Appaddurai I, et al: Zopiclone as a preoperative night hypnotic: a double-blind comparison with temazepam and placebo. *Br J Anaesth* 1994; 72:443-446.
- 201 Padfield NL, Twohig M Mc D, & Fraser ACL: Temazepam and trimeprazine compared with placebo as premedication in children: an investigation extended into the first 2 weeks at home. *Br J Anaesth* 1986; 58:487-493.
- 202 Thomas DL, Vaughan RS, Vickers MD, et al: Comparison of temazepam elixir and trimeprazine syrup as oral premedication in children undergoing tonsillectomy and associated procedures. *Br J Anaesth* 1987; 59:424-430.
- 203 Dorward AJ, Berkin KE, Elliott JA, et al: A double-blind controlled study comparing temazepam with papaveretum as premedication for fiberoptic bronchoscopy. *Br J Dis Chest* 1983; 77:60-65.
- 204 Greenblatt DJ, Harmatz JS, Engelhardt N, et al: Pharmacokinetic determinants of dynamic differences among three benzodiazepine hypnotics. *Arch Gen Psychiatry* 1989; 46:326-332.
- 205 Rush CR, Higgins ST, Hughes JR, et al: A comparison of the acute behavioral effects of triazolam and temazepam in normal volunteers. *Psychopharmacology* 1993; 112:407-414.
- 206 Kales A, Bixler EO, Soldatos CR, et al: Quazepam and temazepam: effects of short- and intermediate-term use and withdrawal. *Clin Pharmacol Ther* 1986; 39:345-352.
- 207 Priest RG & Rizvi ZA: Temazepam comparable to nitrozeepam as a hypnotic. *J Int Med Res* 1976; 4:145.
- 208 Tedeschi G, Griffiths AN, Smith AT, et al: The effect of repeated doses of temazepam and nitrazepam on human psychomotor performance. *Br J Clin Pharm* 1985; 20:361-367.
- 209 Allen RP, Mendels J, Nevins DB, et al: Efficacy without tolerance or rebound insomnia for midazolam and temazepam after use for one to three months. *J Clin Pharmacol* 1987; 27:768-775.
- 210 Nightingale JJ & Norman J: A comparison of midazolam and temazepam for premedication of day case patients. *Anaesthesia* 1988; 43:111-113.
- 211 Fisher RJH & Dean BC: A multi-centre, double-blind trial in general practice comparing the hypnotic efficacy and event profiles of flunitrazepam and temazepam. *Pharmatherapeutica* 1985; 4:231-235.

- 212 Irjala J, Kanto J, Irjala K, et al: Temazepam versus flunitrazepam as an oral premedication in adult surgical patients. *Eur J Anaesthesiol* 1987; 4:435-440.
- 213 O'Boyle CA, Harris D, & Barry H: Sedation in outpatient oral surgery. *Br J Anaesth* 1986; 58:378-384.
- 214 Van Steenis D: A comparison of chlormezanone and temazepam in sleep disturbance. *Curr Med Res Opin* 1982; 8:28-32.
- 215 Shull HJ, Wilkinson GR, Johnson R, et al: Normal disposition of oxazepam in acute viral hepatitis and cirrhosis. *Ann Intern Med* 1976; 84:420.
- 216 Greenblatt DJ: Pharmacokinetics in clinical medicine: oxazepam versus other benzodiazepines. *Dis Nerv Syst* 1975; 36:6.
- 217 Gilman AG, Goodman LS, Rall TW, et al (Eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 7th. Macmillan Publishing Co, New York, NY, 1985.
- 218 Greenblatt DJ & Shader RI: Drug therapy: benzodiazepines. *N Engl J Med* 1974; 291:1011.
- 219 Sonne J, Andreasen PB, Loft S, et al: Glucuronidation of oxazepam is not spared in patients with hepatic encephalopathy. *Hepatology* 1990; 11:951-956.
- 220 Anderson PO, Knoben JE, & Troutman WG: *Handbook of Clinical Drug Data*, 9th. Appleton & Lange, Stamford, CT, 1999.
- 221 Young LY & Koda-Kimble MA (Eds): *Applied Therapeutics: The Clinical Use of Drugs*, 6th. Applied Therapeutics, Inc, Vancouver, WA, 1995.
- 222 Verbeek R: Biotransformation and excretion of lorazepam in patients with chronic renal failure. *Br J Clin Pharmacol* 1976; 3:1033.
- 223 Greenblatt DJ: Lorazepam kinetics in the elderly. *Clin Pharmacol Ther* 1979; 26:103.
- 224 Kraus JW: Effects of aging and liver disease on disposition of lorazepam. *Clin Pharmacol Ther* 1978; 24:411.
- 225 Peppers MP: Benzodiazepines for alcohol withdrawal in the elderly and in patients with liver disease. *Pharmacotherapy* 1996; 16:49-58.
- 226 Bakti G, Fisch HU, Karlaganis G, et al: Mechanism of the excessive sedative response of cirrhotics to benzodiazepines: model experiments with triazolam. *Hepatology* 1987; 7:629-638.
- 227 Bass NM & Williams RL: Guide to drug dosage in hepatic disease. *Clin Pharmacokinet* 1988; 15:396-420.
- 228 Klotz U, Avant GR, Hoyumpa A, et al: The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest* 1975; 55:347.
- 229 Andreasen PB, Hendel J, Greisen G, et al: Pharmacokinetics of diazepam in disordered liver function. *Eur J Clin Pharmacol* 1976; 10:115-120.
- 230 Rodighiero V: Effects of liver disease on pharmacokinetics (review). *Clin Pharmacokinet* 1999; 37:399-431.
- 231 Grossman F: A review of anticonvulsants in treating agitated demented elderly patients. *Pharmacotherapy* 1998; 18(3):600-606.
- 232 Class CA, Schneider L, & Farlow MR: Optimal management of behavioural disorders associated with dementia. *Drugs Aging* 1997; 10(2):95-106.
- 233 Rabins PV, Blacker D, Rovner BW, et al: American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; 164(12 Suppl):5-56. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 234 U.S. Food and Drug Administration: Conventional Antipsychotics - Healthcare Professional Sheet text version. U.S. Food and Drug Administration. Rockville, MD. 2009. Available from URL: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm>. As accessed 2009-06-23.
- 235 Meeks TW & Jeste DV: Beyond the Black Box: What is The Role for Antipsychotics in Dementia?. *Curr Psychiatr* 2008; 7(6):50-65. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 236 Lanctot KL, Best TS, Mittmann N, et al: Efficacy and safety of neuroleptics in behavioral disorders associated with dementia. *J Clin Psychiatry* 1998; 59(10):550-561. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 237 Borson S & Raskind MA : Clinical features and pharmacologic treatment of behavioral symptoms of Alzheimer's disease. *Neurology* 1997; 48(5 Suppl 6):S17-S24. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 238 Mintzer JE, Hoernig KS, & Mirski DF: Treatment of agitation in patients with dementia. *Clin Geriatr Med* 1998; 14(1):147-175.
- 239 Verma SD, Davidoff DA, & Kambhampati KK: Management of the agitated elderly patient in the nursing home: the role of the atypical antipsychotics. *J Clin Psychiatry* 1998; 59(suppl 19):50-55.
- 240 Tariot PN: Treatment of agitation in dementia. *J Clin Psychiatry* 1999; 60(suppl):11-20.
- 241 Herrmann N: Valproic acid treatment of agitation in dementia. *Can J Psychiatry* 1998; 43:69-72.
- 242 Rita Moretti, MD, Universita degli Studi di Trieste
- 243 Pollock BG & Mulsant BH: Behavioral disturbances of dementia. *J Geriatr Psychiatry Neurol* 1998; 11:206-212.
- 244 Nyth AL, Gottfries CG, Lyby K, et al: A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. *Acta Psychiatr Scand* 1992; 86:138-145.
- 245 Nyth AL & Gottfries CG: The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders: a Nordic multicentre study. *Br J Psychiatry* 1990; 157:894-901.
- 246 Serra-Mestres J, Shapleske J, & Tym E: Treatment of palilalia with trazodone (letter). *Am J Psychiatry* 1996; 153:580-581.
- 247 Raskind MA, Cyrus PA, Ruzicka BB, et al: The effects of Metrifonate on the cognitive, behavioral, and functional performance of Alzheimer's Disease in patients. *J Clin Psychiatry* 1999; 60:318-325.
- 248 Shelton PS & Brooks VG: Estrogen for dementia-related aggression in elderly men. *Ann Pharmacother* 1999; 33:808-812.
- 249 Barry PJ, Gallagher P, Ryan C, et al: START (screening tool to alert doctors to the right treatment)--an evidence-based screening tool to detect prescribing omissions in elderly patients. *Age Ageing* 2007; 36(6):632-638. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 250 Gallagher P, Ryan C, Byrne S, et al: STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther* 2008; 46(2):72-83. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 251 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria (Supplementary Data). *Age Ageing* 2008; 37(6):1.
- 252 American Geriatrics Society 2012 Beers Criteria Update Expert Panel: American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2012; 60(4):616-631. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>

- 253 Gallagher P & O'Mahony D: STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. *Age Ageing* 2008; 37(6):673-679. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 254 January CT, Wann LS, Alpert JS, et al: 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; Epub:Epub. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 255 Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128(16):e240-e327. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 256 Weber MA, Schiffrin EL, White WB, et al: Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. *J Clin Hypertens (Greenwich)* 2014; 16(1):14-26. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 257 Khanna D , Fitzgerald JD , Khanna PP , et al: 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)* 2012; 64(10):1431-1446. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 258 Hsieh C: Treatment of constipation in older adults. *Am Fam Physician* 2005; 72(11):2277-2284. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 259 Jneid H, Anderson JL, Wright RS, et al: 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2012; 126(7):875-910. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 260 Kearon C, Akl EA, Comerota AJ, et al: Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 suppl):e419S-e494S. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 261 Baldwin DS, Waldman S, & Allgulander C: Evidence-based pharmacological treatment of generalized anxiety disorder. *Int J Neuropsychopharmacol* 2011; 14(5):697-710. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 262 Davidson JR: First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry* 2009; 70 Suppl 2:25-31. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 263 Schutte-Rodin S, Broch L, Buysse D, et al: Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008; 4(5):487-504. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 264 Guerrant RL, Van Gilder T, Steiner TS, et al: Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001; 32(3):331-351. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 265 Talley NJ & Vakil N: Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005; 100(10):2324-2337. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 266 Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD).

- Bethesda, MD. 2013. Available from URL: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013Feb13.pdf. As accessed 2014-08-12.
- 267 Bhatt DL, Scheiman J, Abraham NS, et al: ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; 118(18):1894-1909. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 268 Zhang W, Moskowitz RW, Nuki G, et al: OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008; 16(2):137-162. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 269 American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; 46(2):328-346. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 270 Lucas MG; Bedretdinova D; Bosch JLHR et al: Guidelines on urinary incontinence. European Association of Urology. Arnhem, Netherlands. 2014. Available from URL: http://www.uroweb.org/gls/pdf/20%20Urinary%20Incontinence_LR.pdf. As accessed 2014-08-13.
- 271 World Health Organization (WHO): WHO's cancer pain ladder for adults. World Health Organization (WHO). Geneva, Switzerland. 2014. Available from URL: <http://www.who.int/cancer/palliative/painladder/en/>. As accessed 2014-08-12.
- 272 Schweizer E & Rickels K: Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. *Acta Psychiatr Scand* 1998; 98(suppl 393):95-101.
- 273 Lader M: Withdrawal reactions after stopping hypnotics in patients with insomnia. *CNS Drugs* 1998; 10(6):425-440.
- 274 Hardman JS, Rall TW, Nies AS, et al (Eds): Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th. Pergamon Press, New York, NY, 1996.
- 275 Alexander B & Perry PJ: Detoxification from benzodiazepines: schedules and strategies *J sub Abuse Treat* 1991; 8:9-17. Detoxification from benzodiazepines: schedules and strategies *J sub Abuse Treat* 1991; 8:9-17.
- 276 Brenner PM, Wolf B, Rechlin Th, et al: Benzodiazepine dependence: detoxification under standardized conditions *Drug and Alcohol Dependence* 1991; 29:195-204. Benzodiazepine dependence: detoxification under standardized conditions *Drug and Alcohol Dependence* 1991; 29:195-204.
- 277 DuPont RL: A Physician's guide to discontinuing benzodiazepine therapy *West J Med* 1990; 152:600-603. A Physician's guide to discontinuing benzodiazepine therapy *West J Med* 1990; 152:600-603.
- 278 Rickels K, Case WG, Schweizer E, et al: Benzodiazepine dependence: management of discontinuation *Psychopharmacology Bulletin* 1990; 26:63-68. Benzodiazepine dependence: management of discontinuation *Psychopharmacology Bulletin* 1990; 26:63-68.
- 279 Morin CM, Bastien C, & Guay B: Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 2004; 161(2):332-342.
- 280 Voshaar RO, Gorgels W, Mol A, et al: Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry* 2003; 182:498-504.
- 281 Anon: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30(1):119-141.
- 282 Ballenger JC, Davidson JR, Lecrubier Y, et al: Consensus statement update on posttraumatic stress disorder from the international consensus group on depression and anxiety. *J Clin Psychiatry* 2004; 65:55-62.

- 283 McGregor C, Machin A, & White JM: In-patient benzodiazepine withdrawal: comparison of fixed and symptom-triggered taper methods. *Drug Alcohol Rev* 2003; 22(2):175-180.
- 284 Baillargeon L, Landreville P, Verreault R, et al: Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ* 2003; 169(10):1015-1020.
- 285 Rickels K, DeMartinis n, Rynn M, et al: Pharmacologic strategies for discontinuing benzodiazepine treatment. *J Clin Psychopharmacol* 1999; 19(6 suppl 2):12S- 16S.
- 286 Anderson KE, Bloomer JR, Bonkovsky HL, et al: Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; 142(6):439-450. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 287 European Porphyria Initiative: Recommendations for the use of drugs in the acute porphyrias (AIP, HCP, VP). European Porphyria Initiative. Available from URL: <http://www.porphyria-europe.org>. As accessed 2/13/06.
- 288 Moore MR & Hift RJ: Drugs in the acute porphyrias--toxicogenetic diseases. *Cell Mol Biol (Noisy-le-grand)* 1997; 43(1):89-94. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 289 Beers MH, Ouslander JG, Rollinger I, et al: Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med* 1991; 151(9):1825-1832. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 290 Beers MH: Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; 157(14):1531-1536. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 291 Fick DM, Cooper JW, Wade WE, et al: Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med* 2003; 163(22):2716-2724. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 292 Chutka DS, Takahashi PY, & Hoel RW: Inappropriate medications for elderly patients. *Mayo Clin Proc* 2004; 79(1):122-139. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 293 Jano E & Aparasu RR: Healthcare outcomes associated with beers' criteria: a systematic review. *Ann Pharmacother* 2007; 41(3):438-447. PubMed Abstract: <http://www.ncbi.nlm.nih.gov/...> PubMed Article: <http://www.ncbi.nlm.nih.gov/...>
- 294 Product Information: TRANXENE T-TAB(R) oral tablets, clorazepate dipotassium oral tablets. Lundbeck Inc, Deerfield, IL, 2010.
- 295 Product Information: LIBRIUM(R) oral capsules, chlordiazepoxide HCl oral capsules. Valeant Pharmaceuticals International, Costa Mesa, CA, 2005.
- 296 Product Information: XANAX(R) oral tablets, alprazolam oral tablets. Pharmacia & Upjohn Co (per FDA), New York, NY, 2011.
- 297 Product Information: XANAX(R) XR oral extended-release tablets, alprazolam oral extended-release tablets. Pharmacia & Upjohn Co (per FDA), New York, NY, 2011.
- 298 Product Information: KLONOPIN(R) TABLETS, KLONOPIN(R) WAFERS oral tablets, orally disintegrating tablets, clonazepam oral tablets, orally disintegrating tablets. Genentech USA, Inc, South San Francisco, CA, 2010.
- 299 Product Information: VALIUM(R) oral tablets, diazepam oral tablets. Roche Laboratories Inc, Nutley, NJ, 2008.
- 300 Product Information: estazolam oral tablets, estazolam oral tablets. Watson Laboratories, Inc., Corona, CA, 2008.
- 301 Product Information: DORAL(R) oral tablets, quazepam oral tablets. Questcor Pharmaceuticals, Inc., Union City, CA, 2007.

- 302 Product Information: DALMANE(R) oral capsules, flurazepam hydrochloride oral capsules. Valeant Pharmaceuticals North America, Aliso Viejo, CA, 2007.
- 303 Product Information: lorazepam oral tablets, lorazepam oral tablets. Watson Laboratories, Inc., Corona, CA, 2008.
- 304 Product Information: oxazepam oral capsule, oxazepam oral capsule. Actavis Elizabeth LLC, Elizabeth, NJ, 2007.
- 305 Product Information: Restoril(TM) oral capsules, temazepam oral capsules. Mallinckrodt Inc., Hazelwood, MO, 2010.
- 306 Product Information: HALCION(R) oral tablets, triazolam oral tablets. Pharmacia & Upjohn Company, New York, NY, 2008.
- 307 Institute for Safe Medication Practices: ISMP updates its list of drug name pairs with TALL man letters. Institute for Safe Medication Practices. Horsham, PA. 2010. Available from URL: <http://www.ismp.org/>. As accessed 2010-12-08.
- 308 Institute for Safe Medication Practices: ISMP Medication Safety Alert: Community/Ambulatory Care Edition. Institute for Safe Medication Practices. Horsham, PA. 2008. Available from URL: <http://www.ismp.org/>. As accessed 2008-12-01.
- 309 Institute for Safe Medication Practices: ISMP's List of Confused Drug Names. Institute for Safe Medication Practices. Horsham, PA. 2009. Available from URL: <http://www.ismp.org/>. As accessed 2009-09-14.

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

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