

DRUGDEX-EV 0111

MICROMEDEX

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CLONAZEPAM

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0.0] Overview

1) Class

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

Antianxiety
Anticonvulsant

2) Dosing Information

a) Adult

1) [Panic disorder](#)

- a) initial, 0.25 mg ORALLY twice daily for 3 days, then increased to a target dose of 1 mg daily [13] [14]
- b) maintenance, may increase dosage by 0.125 to 0.25 mg ORALLY twice daily every 3 days to a MAX total daily dose of 1 to 4 mg [13] [14]
- c) discontinuation, decrease dose by 0.125 mg twice daily every 3 days [13] [14]

2) Seizure

- a) initial, 0.5 mg ORALLY 3 times a day [14] [13]
- b) maintenance, may increase daily dose by 0.5 to 1 mg ORALLY every 3 days to a MAX total daily dose of 20 mg (divided into 3 daily doses) [14] [13]

b) Pediatric

- 1) safety and effectiveness not established in the treatment of [panic disorder](#) in pediatric patients younger than 18 years [14] [13]

a) Seizure

1)) (up to 10 years or up to 30 kg) initial, 0.01 to 0.03 mg/kg/day ORALLY divided into 2 to 3 daily doses; MAX 0.05 mg/kg/day divided into 2 or 3 daily doses [14] [13]

2)) (up to 10 years or up to 30 kg) maintenance, may increase daily dose by 0.25 to 0.5 mg ORALLY every 3 days; MAX 0.1 to 0.2 mg/kg/day divided into 3 daily doses [14] [13]

3) Contraindications

a)) acute [narrow angle glaucoma](#) [51]

b)) hypersensitivity to benzodiazepines [51]

c)) significant liver disease [51]

4) Serious Adverse Effects

a)) Depression

b)) [Respiratory depression](#)

c)) Suicidal thoughts

5) Clinical Applications

a)) FDA Approved Indications

1)) [Panic disorder](#)

2)) Seizure

1.0] Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult Dosage](#)

[Pediatric Dosage](#)

1.1] Drug Properties

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

B)) Synonyms

[Clonazepam](#)

C)) Orphan Drug Status

1)) [Clonazepam](#) has been designated an orphan product for use in the treatment of hyperekplexia (startle disease).

D)) Physicochemical Properties

1)) Molecular Weight

a) 315.72 [357]

2) pKa

a) pK1: 1.5; pK2: 10.5 [358]

3) Solubility

a) Insoluble in water; slightly soluble in alcohol and in ether; sparingly soluble in acetone and in chloroform [359]

1.2] Storage and Stability

A) Preparation

1) Oral route

a) Oral Tablets

1) Swallow oral tablets whole with water [14].

b) Orally Disintegrating Tablets

1) Open the pouch and peel back the foil on the blister pack; do not push the tablet through the foil. Using dry hands, immediately remove the tablet and place it in the mouth. It will dissolve quickly and be easily swallowed with or without water [13].

B) Oral route

1) Tablet/Tablet, Disintegrating

a) Store at 25 degrees C (77 degrees F) with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [51] [15]

C) Extemporaneous Formulation - Oral route

1) A clonazepam 0.1 mg/mL suspension, 60 mL, may be prepared using 6 clonazepam 1 mg tablets (Klonopin(R); Roche), distilled water to levigate, Cologel(R) (methylcellulose; Lilly) 15 mL, and a sufficient quantity of a 2:1 simple syrup/cherry syrup mixture to bring the volume to 60 mL. This mixture should be labeled "shake well" and "refrigerate" and is stable for 5 days [360].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Oral route

1.3.1.A.1] Panic disorder

a) For panic disorder, the initial recommended dose is clonazepam 0.25 mg twice daily. The dose may be increased after 3 days in increments of 0.125 mg to 0.25 mg twice daily. The target dose for

most patients is 1 mg/day. In studies, higher doses of 2, 3, and 4 mg/day were less effective than 1 mg/day, but some individuals may benefit from doses up to a maximum of 4 mg/day. For patients who need higher doses, increases in increments of 0.125 to 0.25 mg twice daily every 3 days may be used until control of [panic disorder](#) or development of intolerable side effects. Administration of 1 of the doses at bedtime may reduce the inconvenience of somnolence. Gradually discontinue treatment by decreasing the dose by 0.125 mg twice daily every 3 days [14] [13].

1.3.1.A.2] Seizure

a) For seizure disorder, the initial dose for adults should not exceed 1.5 mg/day divided into 3 doses. Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase [14] [13].

b) The maintenance dosage for seizure disorder must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg [14] [13].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Oral route

1.4.1.A.1] Seizure

a) In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be 0.01 to 0.03 mg/kg/day, not to exceed 0.05 mg/kg/day, given in 2 or 3 divided doses [14] [13].

b) Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg/day has been reached unless seizures are controlled or side effects preclude further increase [14] [13].

c) Whenever possible, the daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given before retiring [14] [13].

1.4.1.B] The safety and effectiveness of [clonazepam](#) have not been established in the treatment of [panic disorder](#) in pediatric patients younger than 18 years [14] [13].

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

A) Onset

1) Initial Response

a) SEIZURES, ORAL, 20 and 40 minutes [230].

B) Duration

1) Single Dose

a) SEIZURES, ORAL, 6 to 12 hours [230].

1J) Single dose duration of action was 6 to 8 hours in infants and younger children [230].

2J) A satisfactory clinical effect usually occurs quickly, from after the first dose to within the first weeks of treatment (Munthe-Kass, 1973) [231] [232].

2.2] Drug Concentration Levels

AJ) Therapeutic Drug Concentration

1J) SEIZURES, 25 to 30 ng/mL [236].

aJ) Lower plasma levels (20 ng/mL or less) control myoclonic and self-induced [photogenic epilepsy](#) [236].

bJ) The relationship between plasma levels and the dose is linear [236] [237].

BJ) Time to Peak Concentration

1J) ORAL, 1 to 4 hours [233] [234].

2J) RECTAL, 10 to 30 minutes [235].

2.3] ADME

2.3.1] Absorption

AJ) Bioavailability

1J) 90% [233].

2.3.2] Distribution

AJ) Distribution Sites

1J) Protein Binding

aJ) 85% [233].

1J) Clonazepam plasma protein binding in four groups (healthy volunteers, cirrhotic patients, uremic patients before and after hemodialysis and patients with poor renal function), consisting of six subjects each, was 13.9%, 17.1%, 15.6% and 12.2% and 16.0%, respectively. The figure of healthy volunteers significantly differed only from that of the cirrhotic patient. Clonazepam bound preferentially to albumin [239].

BJ) Distribution Kinetics

1J) Volume of Distribution

aJ) 3.2 L/kg [240].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics**1) Liver, highly metabolized [233].**

a) The rate of N-acetylation is dependent upon acetylator phenotype [241].

b) The major route is via cytochrome P-450 including CYP3A [233].

2.3.4] Excretion**A) Kidney****1) Renal Excretion (%)**

a) 0.5% to 1% [242] [240].

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

1) ELIMINATION HALF-LIFE, 30 to 40 hours [233] [240].

2) Serum half-lives ranged from 22 to 33 hours (mean 28.7 hours) in children [237].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.1] Contraindications

A) acute [narrow angle glaucoma](#) [51]

B) hypersensitivity to benzodiazepines [51]

C) significant liver disease [51]

3.2] Precautions

A) Endocrine and Metabolic:

B) -- phenylketonurics; orally disintegrating tablets contain [phenylalanine](#) [51]

C) Neurologic:

D) -- [status epilepticus](#) may occur upon abrupt withdrawal, particularly in patients on long-term, high-dose therapy; gradual withdrawal recommended [51]

E) -- may worsen seizure disorder (ie, increased incidence or precipitated onset of grand mal seizures); addition of anticonvulsants or dosage increases may be required [51]

F) Psychiatric:

G) -- suicidal thoughts or behavior risk increase has been reported; monitoring recommended [51]

H) Renal:

I) -- use caution in patients with [renal impairment](#) since [clonazepam](#) metabolites are renally excreted [51]

J) Reproductive:

K) -- use caution in pregnant patients due to risk for [birth defects](#), especially during first trimester [51]

L) Respiratory:

M) -- patients with chronic respiratory disease may experience increased salivation and potential for [respiratory depression](#) [51]

N) Other:

O) -- withdrawal symptoms have occurred following discontinuation [51]

P) -- patients with history of drug dependence may be at risk for drug abuse [51]

Q) -- monitor CBC and liver function with prolonged use [51]

R) -- may interfere with cognitive and motor performance, therefore, use caution with hazardous occupations (eg, as operating machinery or driving a motor vehicle) [51]

S) Concomitant use:

T) -- avoid alcohol use [51]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Palpitations

1) Palpitations have occurred in patients receiving [clonazepam](#) for seizure disorders [15].

3.3.2] Dermatologic Effects

3.3.2.A] Hirsutism

1) Hirsutism has been reported in patients receiving [clonazepam](#) for seizures disorders [15].

3.3.2.B] Loss of hair

1) Hair loss has been reported in patients receiving [clonazepam](#) for seizure disorders [15].

3.3.2.C] Rash

1) Skin rash has been reported in patients receiving [clonazepam](#) for seizure disorders [15].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Acute intermittent porphyria, Exacerbation

1) Exacerbation of [acute intermittent porphyria](#) with an increase in seizure frequency was reported in a patient who received high [clonazepam](#) doses (20 mg) [60].

3.3.4] Gastrointestinal Effects

3.3.4.A] Burning mouth syndrome

1) A 52-year-old woman developed burning mouth syndrome 4 weeks after beginning [clonazepam](#) 0.5 milligrams (mg) twice daily for anxiety and panic symptoms. Discontinuation of [alprazolam](#) and initiation of [clonazepam](#) had been the only changes to her chronic medications. With continued use of [clonazepam](#), the burning mouth symptoms worsened. Decreasing her dose to 0.25 mg twice daily reduced symptoms somewhat, but they remained intolerable. Three weeks after discontinuation of [clonazepam](#), the burning mouth symptoms resolved. Other drugs for treatment of anxiety and panic were tried but were not effective. The patient requested a repeat trial of [clonazepam](#). After 2 weeks, she again experienced intolerable mouth

burning. [Clonazepam](#) was discontinued after 4 weeks, and burning mouth symptoms resolved within 2 to 3 weeks. ([Clonazepam](#) has been used, with some success, for treatment of burning mouth syndrome.) [61].

3.3.4.B| Constipation

1) Constipation has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.4.C| Diarrhea

1) Diarrhea has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.4.D| Gastritis

1) [Gastritis](#) has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.4.E| Loss of appetite

1) Anorexia has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.4.F| Nausea

1) Nausea has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.4.G| Weight increased

1) A weight gain of 20% or more of the original body weight, invariably the result of [hyperphagia](#), has been reported [56].

2) Weight gain was reported in 10 of 10 patients receiving [clonazepam](#) for absence seizures. Weight gain became noticeable by the 8th week of therapy [59].

3.3.4.H| Xerostomia

1) Dry mouth has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.5| Hematologic Effects

3.3.5.A| Thrombocytopenia

1) [Thrombocytopenia](#) secondary to [clonazepam](#) was reported in a 52-year-old female following doses of 0.5 to 1 mg twice a day for an unknown length of time. The patient developed [epistaxis](#) and [purpura](#), with a corresponding [platelet](#) count of 6000/cu mm³. The [platelet](#) count gradually increased to over 150,000/cu mm³ with discontinuation of the drug and [prednisone](#) therapy [52].

2) [Thrombocytopenia](#) has occurred with other benzodiazepine derivatives (Swanson and Cook, 1977), and similar effects should be expected from [clonazepam](#) administration.

3.3.6| Hepatic Effects

3.3.6.A| Hepatomegaly

1) Hepatomegaly has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.6.B| Hepatotoxicity

1) Transient elevations of serum transaminases and [alkaline phosphatase](#) have been reported [15], but one worker reported a decrease in previously elevated serum [alkaline phosphatase](#) levels [55].

3.3.8] Musculoskeletal Effects

3.3.8.A] Myalgia

- 1) Incidence: 4% [15]
- 2) Myalgia was reported in 4% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 3% of 294 patients receiving placebo during clinical trials [15].

3.3.8.B] Poor muscle tone

- 1) Hypotonia has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.9] Neurologic Effects

3.3.9.A] Aphonia

- 1) Aphonia has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.9.B] Ataxia

- 1) Incidence: 5% to 30% [15]
- 2) Experience to date has shown that ataxia has occurred in approximately 30% of patients treated for seizure disorders. This may diminish in time in some cases [15].
- 3) Ataxia was reported in 5% of 574 patients receiving [clonazepam](#) therapy for [panic disorder](#) compared with 0% of 294 patients receiving placebo during clinical trials [15].

3.3.9.C] Confusion

- 1) Confusion has been reported in patients receiving [clonazepam](#) for seizure disorders [15].

3.3.9.D] Coordination problem

- 1) Incidence: 6% [15]
- 2) Abnormal coordination was reported in 6% of 574 patients receiving [clonazepam](#) therapy for [panic disorder](#) compared with 0% of 294 patients receiving placebo during clinical trials [15].

3.3.9.E] Dizziness

- 1) Incidence: 8% [15]
- 2) Vertigo has been reported in patients treated with [clonazepam](#) for seizure disorders [15].
- 3) Dizziness was reported in 8% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 4% of 294 patients receiving placebo during clinical trials [15].

3.3.9.F] Dysarthria

- 1) Incidence: 2% [15]
- 2) [Dysarthria](#) has been reported in patients treated with [clonazepam](#) for seizure disorders [15].
- 3) [Dysarthria](#) was reported in 2% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 0% of 294 patients receiving placebo during clinical trials [15].

3.3.9.G] Dysdiadochokinesis

- 1) Dysdiadochokinesis has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.9.H] Headache

1) Headache has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.9.I] Intelligence finding

1) Incidence: 2% [15]

2) Reduced intellectual ability was reported in 2% of 574 patients receiving [clonazepam](#) therapy for [panic disorder](#) compared with 0% of 294 patients receiving placebo during clinical trials [15].

3.3.9.J] Memory impairment

1) Incidence: 4% [15]

2) [Memory disturbance](#) was reported in 4% of 574 patients receiving [clonazepam](#) therapy for [panic disorder](#) compared with 2% of 294 patients receiving placebo during clinical trials [15].

3.3.9.K] Seizure

1) [Clonazepam](#) has been implicated in the aggravation or precipitation of grand mal seizures [53]; (Scollo-Lavizzari, 1974) [54]. An improvement in minor seizures, but persistence of nocturnal major motor seizures has been noted [55]. Some workers described the development of a new seizure type after [clonazepam](#) therapy [56] [57], but other studies have noted no increase in the frequency of seizures or the development of a new type of seizure [58] [59].

3.3.9.L] Slurred speech

1) Slurred speech has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.9.M] Somnolence

1) Incidence: 37% to 50% [15]

2) Experience to date has shown that drowsiness has occurred in approximately 50% of patients treated for seizure disorders. This may diminish in time in some cases [15].

3) Drowsiness was reported in 37% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 10% of 294 patients receiving placebo during clinical trials [15].

3.3.9.N] Tremor

1) Tremor has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.10] Ophthalmic Effects**3.3.10.A] Diplopia**

1) [Diplopia](#) has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.10.B] Nystagmus

1) Abnormal eye movements and [nystagmus](#) have been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.10.C] Retinopathy

1J) [Retinopathy](#) developed in a 36-year-old woman, weighing 48 kilograms (kg), with a history of [juvenile myoclonic epilepsy](#) treated with [clonazepam](#) 8 milligrams (mg) daily for 8 years following by 6 mg daily for 13 years. Her last ophthalmic exam, performed 10 years prior, was normal. She was not receiving any other medications, nor did she have a family history of retinal degenerative disease. [Funduscopy](#) revealed mild depigmentation of the retinal pigment epithelium throughout the posterior pole bilaterally and corresponding to transmission hyperfluorescence on [fluorescein angiography](#) [63].

3.3.12] Psychiatric Effects

3.3.12.A] Depression

- 1J) Incidence: 7% [15]
- 2J) Depression was reported in 7% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 1% of 294 patients receiving placebo during clinical trials [15].
- 3J) Depression has been reported in patients receiving [clonazepam](#) to treat either seizures [15].

3.3.12.B] [Dissociative disorder](#)

- 1J) Hysteria has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.12.C] [Feeling nervous](#)

- 1J) Incidence: 3% [15]
- 2J) Nervousness has been reported in patients receiving [clonazepam](#) to treat either seizures [15].
- 3J) Nervousness was reported in 3% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 2% of 294 patients receiving placebo during clinical trials [15].

3.3.12.D] [Hallucinations](#)

- 1J) Hallucinations have been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.12.E] [Hyperactive behavior](#)

- 1J) One worker noted that preexisting hyperactivity in children was aggravated by [clonazepam](#) necessitating additional therapy with [dextroamphetamine](#) or [methylphenidate](#) [55].

3.3.12.F] [Problem behavior](#)

- 1J) Incidence: 25% [15]
- 2J) Experience to date has shown that behavior problems have occurred in approximately 25% of patients treated for seizure disorders. This may diminish in time in some cases [15].

3.3.12.G] [Psychotic disorder](#)

- 1J) [Psychosis](#) has been reported in patients treated with [clonazepam](#) for seizure disorders [15].
- 2J) [Psychosis](#) occurred in a 73-year-old woman with no prior psychiatric history who was treated with [clonazepam](#) 3 mg daily for [blepharospasm](#). Episodic hallucinations began in the tenth week of therapy. The psychiatric diagnosis of organic delusion syndrome was made. [Clonazepam](#) dosage was decreased to 2 mg daily, and the hallucinations resolved [64].
- 3J) [Clonazepam](#) 8 mg daily was reported to induce mania in a 41-year-old patient with [chronic schizophrenia](#). Following 2 weeks of [clonazepam](#) in combination with [perphenazine](#), he developed symptoms of restlessness, irritability, insomnia, pressured speech, and euphoria. Following tapering of

clonazepam and treatment with electroconvulsive therapy, his condition returned to baseline. Continued antipsychotic therapy produced no recurrence of mania [65].

4J) Clonazepam provided no additional therapeutic benefit to 13 chronic schizophrenic patients who were already receiving neuroleptic medication [66]. In addition, 2 of the 13 patients demonstrated aggressive behavior during clonazepam withdrawal, and 2 patients became violent while the dosage was being increased.

3.3.12.HJ Suicidal thoughts

1J) A pooled analysis found an increased risk of suicidal behavior or ideation may exist in patients receiving therapy with antiepileptic drugs (AEDs) including clonazepam. The analysis included 199 placebo-controlled clinical studies covering 11 different AEDs used for several different indications such as epilepsy and selected psychiatric illnesses. The analysis included 27,863 patients treated with AEDs and 16,029 patients who received placebo. There were 4 completed suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal behavior or ideation occurred in 0.43% of patients in the AED treatment groups compared to 0.24% of patients in the placebo groups. This represents an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated compared to the placebo groups. Patients treated for epilepsy, psychiatric disorders, or other conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emergence or worsening of depression, suicidality and other unusual changes in behavior, which may include symptoms such as anxiety, agitation, hostility, mania, and hypomania [15].

3.3.13 Renal Effects

3.3.13.AJ Urinary incontinence

1J) Clonazepam therapy resulted in urinary retention in a 2-year-old child with cerebral palsy being treated with valproate and carbamazepine for seizure prevention. As the frequency of seizures increased, clonazepam 0.05 milligrams/kilogram (mg/kg) daily was started. Three days later the patient was admitted to the hospital as urinary retention was noted. Since the condition did not improve after a course of antibiotics, an indwelling catheter was placed. Removal of the catheter 5 days later resulted in urinary retention. Clonazepam was stopped 10 days after initiation and phenobarbital started. Urinary catheterization was not required, but slow emptying noted for the next 2 days followed by resolution of all symptoms (Casken & Odabas, 2004).

2J) Urinary incontinence has been reported in 2 elderly patients who received clonazepam 0.5 mg twice daily for control of essential tremor. Urological examination in both patients was normal. After discontinuation of the drug, urinary symptoms abated within 24 hours. No mechanism for clonazepam-induced urinary retention has been proposed [62].

3.3.14 Reproductive Effects

3.3.14.AJ Increased libido

1J) Increased or decreased libido has been reported in patients treated with clonazepam for seizure disorders [15].

3.3.14.BJ Precocious puberty

1J) Precocious development of secondary sexual characteristics was described in an 15-month-old girl following approximately 2 months of clonazepam therapy (0.5 mg orally twice a day) for convulsions. In addition, the patient had marked behavioral problems while taking clonazepam, and the drug was withdrawn at the age of 17 months, resulting in resolution of secondary sexual characteristics. The authors

propose that [clonazepam](#) may induce sexual precocity secondary to a small rise in sex hormone levels or an alteration in sex hormone-binding proteins [67].

3.3.14.C] Reduced libido

1) Increased or decreased libido has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.15] Respiratory Effects

3.3.15.A] Dyspnea

1) Shortness of breath has been reported in patients treated with [clonazepam](#) seizure disorders [15].

3.3.15.B] Epistaxis

1) [Thrombocytopenia](#) secondary to [clonazepam](#) was reported in a 52-year-old female following doses of 0.5 to 1 mg twice a day for an unknown length of time. The patient developed [epistaxis](#) and [purpura](#), with a corresponding [platelet](#) count of 6000/cu mm 3. The [platelet](#) count gradually increased to over 150,000/cu mm 3 with discontinuation of the drug and [prednisone](#) therapy [52].

3.3.15.C] Nasal discharge

1) Rhinorrhea has been reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.15.D] Respiratory depression

1) [Respiratory depression](#) was reported in patients treated with [clonazepam](#) for seizure disorders [15].

3.3.15.E] Upper respiratory infection

1) Incidence: 8% [15]

2) [Upper respiratory tract infection](#) was reported in 8% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 4% of 294 patients receiving placebo during clinical trials [15].

3.3.16] Other

3.3.16.A] Drug withdrawal

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.B] Fatigue

1) Incidence: 7% [15]

2) Fatigue was reported in 7% of 574 patients receiving [clonazepam](#) for [panic disorder](#) compared with 4% of 294 patients receiving placebo during clinical trials [15].

3.3.16.C] Withdrawal sign or symptom

1) Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepine drugs. These symptoms include convulsions, tremor, abdominal and muscle cramps, vomiting and sweating. Dependence-prone individuals such as drug addicts or alcoholics should be under careful surveillance when receiving benzodiazepines because of the predisposition of such patients to psychological and physical dependence [15].

3.4] **Teratogenicity/Effects in Pregnancy/Breastfeeding**

A) **Teratogenicity/Effects in Pregnancy**

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

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

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

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

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) All benzodiazepines can be expected to cross the placenta. **Teratogenicity** with **clonazepam** has not been confirmed; however, other benzodiazepines have demonstrated teratogenic potential [224]. Thus, use of **clonazepam** during pregnancy is not recommended. If pregnancy occurs during use, the patient should be advised of the desirability of discontinuing the drug and of possible consequences to the fetus [225]. The North American Antiepileptic Drug Pregnancy Registry has been established to evaluate safety outcomes of pregnant women who are receiving antiepileptic therapy. Patients and their healthcare providers are encouraged to enroll by contacting the registry at 1-888-233-2334. To find out more about the North American Antiepileptic Drug Pregnancy Registry, go to <http://www.aedpregnancyregistry.org/> [51].

5) Literature Reports

a) In a case series study of 38 pregnant women who used **clonazepam** for serious **panic disorder**, maternal and fetal outcomes were positive [218]. In this study, women were exposed to a mean daily dose of 1 mg **clonazepam** for a mean of 26.6 weeks. Among infants for whom medical records were available, there were no cases of malformations, neonatal **apnea**, or **clonazepam** withdrawal symptoms. In addition, Apgar scores at 1 and 5 minutes ranged from 6 to 9 and 8 to 10, respectively, for infants with drug exposure at delivery; scores were 7 to 9 and 9 to 10, respectively, for those exposed at other times during the pregnancy. Two babies born to the same mother showed neonatal distress; however, the mother was also exposed to **imipramine**. A single infant was diagnosed with cardiac disease; however, this infant was not exposed to **clonazepam** during the first trimester. One patient with partial complex seizures took 5.5 mg **clonazepam** daily throughout pregnancy; the infant had no external malformations at birth [219].

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 [220].

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. 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 2 case-control studies that each provided conflicting evidence of any association between benzodiazepine exposure and cardiac malformations, and 1 study failed to find an association between exposure and central nervous system defects [221].

d) Although a direct causal relationship could not be established, neonatal toxicity characterized by [apnea](#), hypotonia, and cyanosis, was reported in a 6-hour-old infant following [clonazepam](#) exposure [222]. Neonatal withdrawal symptoms have been reported in infants exposed in utero to other benzodiazepines [223]; such effects were not observed in the aforementioned study [218].

B) Breastfeeding

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

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

2) Clinical Management

a) Human data is lacking regarding the use of [clonazepam](#) during breastfeeding; the manufacturer advises against breastfeeding while on [clonazepam](#) [51] [226]. While the American Academy of Pediatrics identifies a number of benzodiazepines as having unknown effects of possible concern to a nursing infant [228], the World Health Organization considers the benzodiazepine [diazepam](#) safe during lactation when used occasionally and in small doses [229]. This information should be interpreted with caution for women who require chronic [clonazepam](#) therapy for seizure control.

3) Literature Reports

a) The manufacturer indicates that mothers receiving [clonazepam](#) should not breastfeed their infants [51] [226]. Breast milk [clonazepam](#) levels of 11 to 13 ng/mL have been reported in a mother who was receiving [clonazepam](#) [227]. The authors presented no clinical data regarding the effects on the infant after exposure via breast milk; however, the infant had been exposed in utero, and [apnea](#), hypotonia, and cyanosis were present at 6 hours of age.

4) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.3 [227]

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 [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.B] [Amiodarone](#)

1) Interaction Effect: [clonazepam](#) toxicity (confusion, slurred speech, [enuresis](#))

2) Summary: One case has been reported in which symptoms of [clonazepam](#) toxicity (confusion, slurred speech, [enuresis](#)) occurred after two months of concurrent [amiodarone](#) (200 mg daily) and [clonazepam](#) (0.5 mg daily) therapy [116]. These symptoms improved after discontinuing [clonazepam](#), despite a continued exacerbation of CHF. No rechallenge was reported. Until more data are available, clinicians should be aware of a potential interaction between [clonazepam](#) and [amiodarone](#), and should warn patients of possible signs of [clonazepam](#) toxicity.

3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of intoxication (eg, marked sedation, dizziness, ataxia, weakness, decreased cognition or motor performance, slurred speech, [enuresis](#)). If symptoms are present, reduce [clonazepam](#) dose.
- 7) Probable Mechanism: unknown

3.5.1.C] [Amobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.D] [Anileridine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].
- 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 [110].

3.5.1.E] Aprobarrital

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

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].

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 [117] [118] [119] [120] [121].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.F] Buprenorphine

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

2)) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing dose of one or both agents [114].

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 [114].

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

3.5.1.G] Butabarbital

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

2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].

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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.H] Butalbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.I] Carbamazepine

- 1) Interaction Effect: reduced plasma levels of [clonazepam](#)
- 2) Summary: [Clonazepam](#) and [carbamazepine](#) cotherapy has resulted in decreased [clonazepam](#) serum concentrations. This may be a result of [carbamazepine](#) enzyme induction [147] [148]. One study involving [clonazepam](#) administration to epileptic patients maintained on [carbamazepine](#) either alone or

in combination with other anticonvulsants determined that [clonazepam](#) administration did not influence serum concentrations of [carbamazepine](#) [149].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: [Clonazepam](#) levels should be monitored whenever [carbamazepine](#) is added or withdrawn from therapy, or when the [carbamazepine](#) dose is changed. Also monitor the patient for seizure control.

7) Probable Mechanism: induction of CYP3A4-mediated [clonazepam](#) metabolism by [carbamazepine](#)

8) Literature Reports

a) The effect of [carbamazepine](#) on [clonazepam](#) plasma levels during chronic administration were evaluated in seven healthy volunteers [144]. Subjects were given [clonazepam](#) 1 mg once daily for 29 consecutive days, and [carbamazepine](#) 200 mg was coadministered on days 8 to 29. [Clonazepam](#) plasma levels reached a steady-state level prior to the initiation of [carbamazepine](#) therapy. After the addition of [carbamazepine](#), plasma [clonazepam](#) levels decreased over 5 to 15 days to a level 19% to 37% less than their prior steady-state concentrations. [Carbamazepine](#) also reduced [clonazepam](#) half-life. The proposed mechanism for this drug interaction is enzyme induction caused by [carbamazepine](#).

b) The effects of [clonazepam](#) on serum levels of [phenytoin](#), [phenobarbital](#), and [carbamazepine](#) were studied in 22 epileptic patients who were receiving one or two of these drugs [145]. [Clonazepam](#) 4 mg to 6 mg daily was added to their therapeutic regimens and anticonvulsant levels were determined weekly for at least six weeks. Of the nine patients receiving [carbamazepine](#) either as monotherapy or combined with another anticonvulsant, [carbamazepine](#) plasma concentrations averaged 8.1 mcg/mL prior to [clonazepam](#) and 8.3 mcg/mL after [clonazepam](#) therapy. The authors concluded that [clonazepam](#) has an insignificant effect on plasma concentrations of [carbamazepine](#).

c) Concurrently administered [clonazepam](#) and [carbamazepine](#) were investigated in epileptic children [146]. The steady-state plasma concentration of [clonazepam](#) was determined in 66 epileptic children who were receiving both [carbamazepine](#) and [clonazepam](#). These levels were compared to the plasma levels of [clonazepam](#) in 188 other children who were receiving [clonazepam](#) as monotherapy. In another group of 12 children, some of whom were included in the previous groups, [carbamazepine](#) was added to their pre-existing regimen of [clonazepam](#). Another group of 11 children was maintained on [clonazepam](#) and [carbamazepine](#), and their therapeutic regimen was changed to [clonazepam](#) alone. All plasma levels were determined four or more weeks after maintaining the same dose and regimen. When comparing the plasma levels of [clonazepam](#), children who received [clonazepam](#) monotherapy had a mean level of 30.9 ng/mL and children who were receiving therapy with [clonazepam](#) and [carbamazepine](#) had a mean level of 26.2 ng/mL. When [carbamazepine](#) was added to [clonazepam](#) monotherapy, steady-state plasma concentrations of [clonazepam](#) decreased from 47.5 ng/mL to 35.1 ng/mL. Conversely, when children who were receiving [clonazepam](#) and [carbamazepine](#) were switched to [clonazepam](#) monotherapy, plasma levels of [clonazepam](#) increased from 28.6 ng/mL to 34.4 ng/mL.

3.5.1.J] [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 [161] [162]. 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 [161] [162]. 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.K] [Carisoprodol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 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] [Ceritinib](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [109].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate [109].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

3.5.1.M] [Chloral Hydrate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: [Chloral](#) hydrate, with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [192]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.N] [Chlorzoxazone](#)

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

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.O] [Cimetidine](#)

- 1) Interaction Effect: [clonazepam](#) toxicity (CNS depression)
- 2) Summary: [Cimetidine](#) decreases the clearance of benzodiazepines that are metabolized by hydroxylation or dealkylation (eg, [diazepam](#), [chlordiazepoxide](#), [clorazepate](#), [flurazepam](#), [prazepam](#), [halazepam](#), [alprazolam](#), [triazolam](#), [midazolam](#), [quazepam](#), [estazolam](#), bromazepam) [87] [88] [89] [90]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [91] [92]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, nitrazepam, [clonazepam](#)) [93] [94]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [95] [96] [97] [98].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce benzodiazepine dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: decreased [clonazepam](#) metabolism

3.5.1.P] [Clarithromycin](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate and risk for toxicity
- 2) Summary: Use caution with coadministration of [clarithromycin](#), a strong CYP3A inhibitor, with drugs extensively metabolized by CYP3A, as increased plasma concentrations of the CYP3A substrate and risk for toxicity may occur. Consider dose adjustments, when possible, and closely monitor serum concentrations of drugs primarily metabolized by CYP3A [160].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [clarithromycin](#) with drugs extensively metabolized by CYP3A, as increased plasma concentrations of the CYP3A substrate and risk for toxicity may occur. Consider dose adjustments, when possible, and closely monitor serum concentrations of drugs primarily metabolized by CYP3A [160].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by [clarithromycin](#)

3.5.1.Q] [Cobicistat](#)

- 1) Interaction Effect: increased [clonazepam](#) exposure
- 2) Summary: Use caution with coadministration of [clonazepam](#) (a CYP3A substrate) with cobicistat (a CYP3A inhibitor), as concurrent use may increase [clonazepam](#) plasma concentrations. Clinical monitoring is recommended with coadministration [115].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of [clonazepam](#) (a CYP3A substrate) with cobicistat (a CYP3A inhibitor), as concurrent use may increase [clonazepam](#) plasma concentrations. Clinical monitoring is recommended with coadministration [115].
- 7) Probable Mechanism: inhibition of CYP3A-mediated [clonazepam](#) metabolism

3.5.1.R] [Codeine](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].
- 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 [110].

3.5.1.S] [Dantrolene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 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.T] [Darunavir](#)

- 1) Interaction Effect: increased CYP3A substrate exposure
- 2) Summary: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. If coadministered, monitor for adverse reactions associated with concomitant drugs [173].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6J) Clinical Management: Use caution with coadministration of [darunavir](#) (a CYP3A inhibitor) with CYP3A substrates. Coadministration may increase CYP3A substrate exposure and increase the risk of clinically significant reactions, including life-threatening or fatal effects. Monitor for adverse reactions associated with concomitant drugs if coadministered [173].

7J) Probable Mechanism: inhibition of CYP3A substrate metabolism

3.5.1.U] [Desipramine](#)

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

2J) Summary: In a case report, the concurrent use of [desipramine](#) and [clonazepam](#) resulted in a decrease in steady state [desipramine](#). This change in [desipramine](#) levels was confirmed by challenge and de-challenge [68].

3J) Severity: moderate

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: [Desipramine](#) levels may be of benefit in patients taking concomitant [clonazepam](#) therapy. Higher doses of [desipramine](#) may be needed if [clonazepam](#) is added, and conversely, the dose of [desipramine](#) may need to be decreased following discontinuation of [clonazepam](#).

7J) Probable Mechanism: increased [desipramine](#) metabolism

3.5.1.V] [Dong Quai](#)

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

2J) Summary: Dong quai extract inhibited metabolism of [diazepam](#) and increased its muscle relaxant effect in rats [195]. 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](#) [195]. It is suspected that dong quai may affect other drugs metabolized by the cytochrome P450 enzymes which metabolize [diazepam](#). Caution is advised.

3J) Severity: moderate

4J) Onset: rapid

5J) Substantiation: theoretical

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

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

8J) Literature Reports

aJ) [Angelica dahurica](#) (dong quai) extract 1 gram/kilogram orally increased the maximum concentration of oral [diazepam](#), yet did not alter pharmacokinetics of intravenous (IV) [diazepam](#) in rats. [Diazepam](#) 5 milligrams/kilogram (mg/kg) was administered orally to rats alone, and one hour after dong quai extract. When administered alone, only the maximum concentration (C_{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 [194].

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 [194].

3.5.1.W] [Ethchlorvynol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [200].
- 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.X] [Evening Primrose](#)

- 1) Interaction Effect: reduced anticonvulsant effectiveness
- 2) Summary: Evening primrose oil contains gamolenic acid (GLA), which may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [106]. Evening primrose oil is contraindicated in patients with [epilepsy](#) [107] [108].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants. Evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the seizure threshold [106].
- 7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.Y] [Fentanyl](#)

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death [189]. 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](#) [113]. 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 [189].
- 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 [189].

7J) Probable Mechanism: additive CNS depression

3.5.1.ZJ [Fluconazole](#)

1J) Interaction Effect: increased [clonazepam](#) exposure and risk for toxicity

2J) Summary: Caution is advised when using [clonazepam](#), a CYP3A4 substrate, together with [fluconazole](#), a moderate CYP3A4 inhibitor, as concomitant use may result in elevated [clonazepam](#) plasma concentrations [210] [207]. Fluconazole-mediated enzyme inhibition may persist for 4 to 5 days after discontinuation [210]. If concomitant use is required monitor closely for clonazepam-associated adverse effects.

3J) Severity: moderate

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Caution is advised when using [clonazepam](#), a CYP3A4 substrate, together with [fluconazole](#), a moderate CYP3A4 inhibitor, as concomitant use may result in elevated [clonazepam](#) plasma concentrations [210] [207]. Fluconazole-mediated enzyme inhibition may persist for 4 to 5 days after discontinuation [210]. If concomitant use is required monitor closely for clonazepam-associated adverse effects.

7J) Probable Mechanism: inhibition of CYP3A4-mediated [clonazepam](#) metabolism by [fluconazole](#)

3.5.1.AA [Fosphenytoin](#)

1J) Interaction Effect: altered concentrations of either drug

2J) Summary: Concurrent use of [clonazepam](#) and [phenytoin](#) has resulted in decreased [phenytoin](#) levels [182], decreased [clonazepam](#) levels [183] [184], and no change in either drug [185].

3J) Severity: minor

4J) Onset: delayed

5J) Substantiation: probable

6J) Clinical Management: Closely monitor any patient receiving combined [phenytoin](#) and [clonazepam](#) therapy for clinical efficacy of both agents; serum [phenytoin](#) levels might also be considered when a benzodiazepine is added or discontinued from therapy.

7J) Probable Mechanism: altered hepatic metabolism of either drug

8J) Literature Reports

aJ) The effect of [phenytoin](#) and [phenobarbital](#) on the disposition of single oral doses of [clonazepam](#) in volunteers was evaluated [179]. Pretreatment with [phenytoin](#) decreased the half-life (31%) and increased the clearance (46% to 58%) of [clonazepam](#). [Phenobarbital](#) produced a lesser effect decreasing the half-life (10%) and increasing the clearance (19% to 24%). Neither drug had an effect on [clonazepam's](#) volume of distribution or plasma protein-binding. The clinical significance of this reported drug interaction is not yet known.

bJ) A study on the effect of [clonazepam](#) on [primidone](#) and [phenytoin](#) plasma levels found [clonazepam](#) to have no effect on [primidone](#) levels in seven patients, an increase in [primidone](#) levels in two patients and a decrease in one patient. The plasma [phenytoin](#) level was increased in nine patients after [clonazepam](#) was introduced, decreased in one and unchanged in three. The increased plasma [phenytoin](#) levels all occurred in patients in whom the previous plasma [phenytoin](#) levels were below the therapeutic range. It is, therefore, uncertain whether the increase was a true effect of [clonazepam](#) or the result of a more regular intake of [phenytoin](#) following closer supervision [180].

c) Eeg-Olofsson suggested that a drug interaction of [clonazepam](#) and [phenytoin](#) occurred in seven children (19% of patients studied) such that the serum concentration of [phenytoin](#) exceeded 20 mcg/mL [181]. However, no further details or explanation of the alleged interactions was given.

3.5.1.AB] 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 [70]. 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.AC] Ginkgo

- 1) Interaction Effect: decreased anticonvulsant effectiveness
- 2) Summary: In a case report, 2 patients with [epilepsy](#) previously well controlled by [valproate](#) sodium developed a recurrence of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn [166]. An infant developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds [167]. The compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as in leaves, the ginkgo component from which commercially available extracts are derived [168]. The majority of ginkgo leaf products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo products are not commonly assayed to assure that 4'-O-methylpyridoxine is not contained in the commercial product. Of concern are those instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-methylpyridoxine may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known seizure disorders).
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with [epilepsy](#). If seizures occur for the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of ginkgo seed or leaf extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxine is present.
- 7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may cause seizures
- 8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine levels. The serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, decreasing to 0.05 mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for the tonic/[clonic convulsions](#) and loss of consciousness observed. They further observed that infants are particularly vulnerable [163].

b)) Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of Ginkgo biloba leaves which is the source of commercially-available products. Highest amounts were found in seeds (85 micrograms (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The albumen of the seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when boiled. The unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was detected in medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O-methylpyridoxine was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingium(R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine of 48.78 mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingium(R), respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba Urtinktur DHU(R) contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the authors note that the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Concern remains with the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested [164].

c)) Seizures recurred in 2 patients, both with [epilepsy](#) that was well controlled prior to ingesting ginkgo biloba (Gb). The patients (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months prior to beginning therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 weeks of beginning Gb therapy, and both remained seizure-free (without changing [anticonvulsant therapy](#)) after discontinuing Gb [165].

3.5.1.AD] [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 [208].

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 [208].

7)) Probable Mechanism: additive CNS depression

3.5.1.AE] [Hydromorphone](#)

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.AF] Idelalisib

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and [midazolam](#) (CYP3A substrate) resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [209].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects [209].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib

8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [209].

3.5.1.AG] 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](#) [142]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [143].

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 [141].

3.5.1.AH] [Ketoconazole](#)

- 1) Interaction Effect: increased [clonazepam](#) exposure
- 2) Summary: Caution is advised when using [clonazepam](#), a CYP3A4 substrate, together with [ketoconazole](#), a strong CYP3A4 inhibitor [206] [207], as concomitant use may result in elevated plasma concentrations resulting in increased or prolonged therapeutic and adverse effects of [clonazepam](#).
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised when using [clonazepam](#), a CYP3A4 substrate, together with [ketoconazole](#), a strong CYP3A4 inhibitor [206] [207], as concomitant use may result in elevated plasma concentrations of [clonazepam](#) resulting in increased or prolonged therapeutic and adverse effects.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [clonazepam](#) by [ketoconazole](#)

3.5.1.AI] [Levorphanol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].
- 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 [110].

3.5.1.AJ] [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 [190] and use with caution [191].
- 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 [190] and use with caution [191].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AK] Magnolia

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Magnolia bark constituents magnolol and honokiol exert central nervous system depression in animals [155] [156] [157]. Effects are likely to be of short duration with a half-life of 49 to 56 minutes observed in rats [158]. The effects of honokiol, an active constituent of magnolia, were reversed following administration of [flumazenil](#) [159]. 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 [150].

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 [151].

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 [152].

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) [153].

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 [154].

3.5.1.AL] 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 [186] [187] [188] 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 [186] [187] [188] 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.AM] Meperidine

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when meperidine and benzodiazepines are used concomitantly. Administration of reduced doses of meperidine is recommended [112]. 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 [113].

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 [110].

3.5.1.AN] Mephenesin

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.AO] Mephobarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.AP] Meprobamate

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

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor for [respiratory depression](#) when these drugs are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.AQ] [Metaxalone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 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] [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 [105].
- 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 [105].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.AS] [Methocarbamol](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [202] [203] [204] [205].
- 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.AT] Methohexital****1) Interaction Effect: additive respiratory depression**

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].

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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.AU] Morphine**1) Interaction Effect: additive respiratory depression**

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.AV] Morphine Sulfate Liposome**1) Interaction Effect: additive respiratory depression**

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.AW] Netupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate

2) Summary: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate due to inhibition of CYP3A4-mediated metabolism by netupitant and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [71].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with the coadministration of netupitant (a CYP3A inhibitor) and a CYP3A substrate, as this may increase plasma concentrations of the CYP3A substrate and increase the risk of adverse effects that may persist for days. Examples of CYP3A substrates include IV administered chemotherapeutic agents and benzodiazepines; close monitoring is recommended of the increased adverse effects of these agents [71].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant

8) Literature Reports

a) [Pharmacokinetic studies](#) demonstrated that coadministration of netupitant 300 mg/[palonosetron](#) 0.5 mg and [docetaxel](#), a chemotherapeutic agents metabolized by CYP3A4, increased [docetaxel](#) Cmax by 49% and AUC by 35%, compared with coadministration with [palonosetron](#) alone. Additionally, coadministration with another chemotherapeutic agent, [etoposide](#), increased [etoposide](#) Cmax and AUC by 10% and 28%, respectively. After a single oral dose of the benzodiazepine [midazolam](#) 7.5 mg was coadministered with netupitant 300 mg, mean Cmax and AUC of [midazolam](#) was 36% and 126% higher, respectively [71].

3.5.1.AX] Nevirapine

1) Interaction Effect: decreased plasma concentrations of [clonazepam](#) or [nevirapine](#)

2) Summary: Use caution with concomitant use of [clonazepam](#) and [nevirapine](#) because of potential decreased exposure and therapeutic effect of both agents. [Nevirapine](#) is an inducer of CYP3A4 enzymes, which are involved in the metabolism of [clonazepam](#). Although studies involving [nevirapine](#) and

clonazepam have not been conducted, monitor virologic response and anticonvulsant levels [104]. Dose adjustments or alternative agents may be required.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Use caution with concomitant use of clonazepam and nevirapine because of potential decreased exposure and therapeutic effect of both agents. Although studies involving nevirapine and clonazepam have not been conducted, monitor virologic response and anticonvulsant levels [104]. Dose adjustments or alternative agents may be required.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of clonazepam by nevirapine

3.5.1.AY] Nilotinib

1) Interaction Effect: increased exposure of CYP3A4 substrate

2) Summary: Use caution when coadministering nilotinib (a CYP3A4 inhibitor) and a CYP3A4 substrate, as this may increase plasma concentrations of the CYP3A4 substrate and increase the risk of adverse effects. During drug interaction studies in patients with chronic myeloid leukemia, coadministration of oral midazolam (a CYP3A4 substrate) and multiple doses of nilotinib resulted in a 2.6-fold increase in midazolam exposure. Because a similar reaction with other CYP3A4 substrates cannot be ruled out, if concurrent use is required, dose adjustments of the CYP3A4 substrate may be necessary, especially for drugs with a narrow therapeutic index [169]. Monitoring for toxicity may also be warranted.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised with the coadministration of nilotinib (a CYP3A4 inhibitor) and a CYP3A4 substrate, as this may increase plasma concentrations of the CYP3A4 substrate and increase the risk of adverse effects. If concurrent use is required, dose adjustments of the CYP3A4 substrate may be necessary, especially for drugs with a narrow therapeutic index [169]. Monitoring for toxicity may also be warranted.

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by nilotinib

8) Literature Reports

a) During drug interaction studies in patients with chronic myeloid leukemia, coadministration of oral midazolam and multiple doses of nilotinib resulted in a 2.6-fold increase in midazolam exposure [169].

3.5.1.AZ] Orlistat

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: Concomitant use of orlistat with anticonvulsant therapy has resulted in reports of convulsions during postmarketing surveillance of orlistat. Therefore, if coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [69].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of orlistat with an anticonvulsant may result in reduced efficacy of the anticonvulsant. If coadministration is necessary, monitor patients for changes in the frequency and severity of their seizures [69].

7) Probable Mechanism: unknown

3.5.1.BA] 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 [174] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [175].
- 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 [174] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [175].
- 7) Probable Mechanism: additive effects

3.5.1.BB] Oxymorphone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].
- 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 [110].

3.5.1.BC] 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 [132]. 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 [132]. 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 [132].

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 [170]. 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 [171]. *Passiflora coerulea* collected in the wild is sometimes adulterated or substituted with the spurious species *Cucurbitella asperata* [172].

3.5.1.BD] [Pentobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].

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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.BE] 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 [201].
- 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 [201].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BF] [Phenobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows

intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.BG| [Phenytoin](#)

- 1) Interaction Effect: altered concentrations of either drug
- 2) Summary: Concurrent use of [clonazepam](#) and [phenytoin](#) has resulted in decreased [phenytoin](#) levels [182], decreased [clonazepam](#) levels [183] [184], and no change in either drug [185].
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Closely monitor any patient receiving combined [phenytoin](#) and [clonazepam](#) therapy for clinical efficacy of both agents; serum [phenytoin](#) levels might also be considered when a benzodiazepine is added or discontinued from therapy.
- 7) Probable Mechanism: altered hepatic metabolism of either drug
- 8) Literature Reports

a) The effect of [phenytoin](#) and [phenobarbital](#) on the disposition of single oral doses of [clonazepam](#) in volunteers was evaluated [179]. Pretreatment with [phenytoin](#) decreased the half-life (31%) and increased the clearance (46% to 58%) of [clonazepam](#). [Phenobarbital](#) produced a lesser effect decreasing the half-life (10%) and increasing the clearance (19% to 24%). Neither drug had an effect on [clonazepam's](#) volume of distribution or plasma protein-binding. The clinical significance of this reported drug interaction is not yet known.

b) A study on the effect of [clonazepam](#) on [primidone](#) and [phenytoin](#) plasma levels found [clonazepam](#) to have no effect on [primidone](#) levels in seven patients, an increase in [primidone](#) levels in two patients and a decrease in one patient. The plasma [phenytoin](#) level was increased in nine patients after [clonazepam](#) was introduced, decreased in one and unchanged in three. The increased plasma [phenytoin](#) levels all occurred in patients in whom the previous plasma [phenytoin](#) levels were below the therapeutic range. It is, therefore, uncertain whether the increase was a true effect of [clonazepam](#) or the result of a more regular intake of [phenytoin](#) following closer supervision [180].

c) Eeg-Olofsson suggested that a drug interaction of [clonazepam](#) and [phenytoin](#) occurred in seven children (19% of patients studied) such that the serum concentration of [phenytoin](#) exceeded 20 mcg/mL [181]. However, no further details or explanation of the alleged interactions was given.

3.5.1.BH| [Primidone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.BI] [Propoxyphene](#)

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.BJ] [Remifentanyl](#)

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

2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.BK] [Ritonavir](#)

- 1)) Interaction Effect: increased [clonazepam](#) serum concentrations and potential toxicity (excessive sedation, confusion)
- 2)) Summary: Coadministered [ritonavir](#) may significantly increase serum concentrations of [clonazepam](#) resulting in [clonazepam](#) toxicity [211].
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Monitor [clonazepam](#) serum levels and follow patients for signs and symptoms of [clonazepam](#) toxicity (excessive sedation, confusion). Reduce doses of [clonazepam](#) as required.
- 7)) Probable Mechanism: decreased [clonazepam](#) metabolism

3.5.1.BL] [Secobarbital](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].
- 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 [117] [118] [119] [120] [121].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [122]. 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 [123]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.BM] [Siltuximab](#)

- 1)) Interaction Effect: decreased effectiveness of CYP3A4 substrate
- 2)) Summary: Coadministration of siltuximab and a CYP3A4 substrate may result in increased metabolism and decreased effectiveness of the substrate. Approach concurrent use with caution. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [193]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 3)) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of siltuximab and a CYP3A4 substrate may increase the metabolism of the substrate and decrease its effectiveness. Use caution when coadministering siltuximab and a CYP3A4 substrate. The effects of siltuximab on CYP450 enzyme activity may persist for several weeks after discontinuation [193]. If coadministration is required, monitoring and dose adjustments may be warranted.
- 7) Probable Mechanism: inhibition of interleukin-6 by siltuximab increases CYP450 levels leading to increased metabolism of CYP450 substrates

3.5.1.BN] 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 [198] [199]. 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 [196].

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](#) [197].

3.5.1.BO] [Sodium Oxybate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [72]. 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.BP] 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 [99] [100] [101] [102]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [99]. 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 [99] [100] [101] [102]. 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 [99].

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) [100].

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 [103].

d) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and C_{max} of oral [midazolam](#) were reduced by 50%, and oral clearance increased 2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [101].

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) [102].

3.5.1.BQ| [Sufentanil](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [111]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [112]. 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](#) [113].

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 [110].

3.5.1.BR] 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 [131].
- 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 [131].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BS] Tan-Shen

- 1) Interaction Effect: increased risk of central nervous system depression
- 2) Summary: Miltirone and the other nine diterpene quinones present in *Salvia miltiorrhiza* (Tan-shen) appear to act as partial agonists at central benzodiazepine receptors [177]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [177]. Because tan-shen acts as a partial and not a full agonist, the clinical significance of the interaction is unknown. Caution is advised until the magnitude of the interaction is better understood.
- 3) Severity: minor
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if tan-shen is used concomitantly with a benzodiazepine. Patients should be advised to avoid operating heavy machinery until the magnitude of the interaction is known.
- 7) Probable Mechanism: partial agonist activity at central benzodiazepine receptors
- 8) Literature Reports

a) Ten diterpene quinones present in the Chinese medicinal herb *Salvia miltiorrhiza* (tan-shen) have been shown to inhibit binding of (3H) flunitrazepam to central benzodiazepine receptors. These quinones, isolated from the ethereal extract of the roots of *Salvia miltiorrhiza*, exhibited

IC50s ranging from 0.3 to 36.2 mcmol (the IC50 is the drug concentration required to provide 50% inhibition of specific (3H) flunitrazepam binding). Miltirone had the highest potency (IC50=0.3 mcmol) [176]. Oral administration of miltirone (10-60 mg/kg) increased the number of punished crossings of mice in the Four-Plate Test which is an indication of clinical tranquilizing effects. The magnitude of this effect was lower than that observed with [diazepam](#) [176].

3.5.1.BT] 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 [178].
- 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 [178].
- 7) Probable Mechanism: additive effects

3.5.1.BU] Theophylline

- 1) Interaction Effect: decreased benzodiazepine effectiveness
- 2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [82] [83] [84] [85]. 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 [86].
- 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 [73].

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 [74]. Other studies and case reports have also shown that theophylline antagonizes the sedative effects of diazepam [75] [76].

c) Three case reports described patients who had the sedative effects of lorazepam reversed postoperatively by the administration of aminophylline 1 mg/kg intravenously [77]. This same aminophylline dose was used to reverse the sedative effects of midazolam in three other patients [78]. Theophylline also was demonstrated to reverse the sedative and psychomotor properties of flunitrazepam in healthy volunteers [79].

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 [80].

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 [81].

3.5.1.BV] Thiopental

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [126] [127] [128] [129] [130].

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 [117] [118] [119] [120] [121].

b) Concomitant administration of intravenous midazolam and thiopental resulted in synergistic (supraadditive) effects during induction of anesthesia [122]. 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 [123]. A 15% reduction in the thiopental induction dose requirement has been observed if it follows

intramuscular premedication with [midazolam](#) [124]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [125].

3.5.1.BW] 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 [132]. Valerian extracts have shown affinity for central and peripheral benzodiazepine receptors as well as barbiturate and GABA-A receptors [140] [133]. Valerian extract displaced the benzodiazepine fluorodiazepam from the receptor [133]. 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 [132]. 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 [132] [133]. 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 [132].

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 [134]

[135]. *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 [136]. 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 [137]. 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 [138].

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* [139].

3.5.1.BX] 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 [212].
- 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 [212].
- 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 clonazepam
- 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 [214] [215] [216].
- 3) Severity: minor
- 4) Onset: rapid
- 5) Substantiation: probable

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

7) Probable Mechanism: central nervous system antagonistic effects

8) Literature Reports

a) Eighteen normal volunteers were randomly studied after receiving 125, 250, or 500 mg of [caffeine](#), both alone and in combination with [lorazepam](#) 2.5 mg, with each subject serving as his own control. Performance testing included critical flicker fusion, verbal learning, digit-symbol substitution, symbol copying, and number cancellation. [Caffeine](#) significantly improved performance on the digit-symbol substitution test when given alone and reduced lorazepam-induced impairment during concurrent administration of both agents. In the symbol copying test, [caffeine](#) counteracted the lorazepam-induced impairment. Although normal subjects were used, [lorazepam](#) induced mood changes characterized as withdrawn, tranquil, and less anxious. The highest dose of [caffeine](#) (500 mg) also counteracted the anti-anxiety effects of [lorazepam](#). The study suggests that only moderate doses of [caffeine](#) should be combined with [lorazepam](#). It further raises the question of the potential effects of [caffeine](#) in patients taking benzodiazepines chronically [213].

3.5.2.B) Ethanol

1) Interaction Effect: increased sedation

2) Summary: Concomitant use of [clonazepam](#) and alcohol may cause increased sedation due to additive CNS depression. Therefore, a patient taking [clonazepam](#) should be advised to avoid the use of alcohol [15].

3) Severity: major

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [clonazepam](#) and alcohol is not recommended. Due to the potential for additive CNS depression with concomitant [clonazepam](#) and alcohol use, a patient who is taking [clonazepam](#) should be advised to avoid alcohol consumption [15].

7) Probable Mechanism: additive CNS depression

4.0] Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

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

4.1] Monitoring Parameters

A) Therapeutic

1) Physical Findings

a) [Panic Disorder](#)

1) A decrease in the intensity of anxiety or frequency of panic attacks indicates efficacy.

b) [Seizure Disorder](#)

1j) A decrease in frequency, severity, and duration of seizures is indicative of efficacy.

Bj) Toxic

1j) Laboratory Parameters

- a) Monitor blood counts periodically during long-term therapy with [clonazepam](#) [51].
- b) Monitor liver function tests periodically during long-term therapy with [clonazepam](#) [51].

2j) Physical Findings

- a) Evaluate patients for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior throughout duration of therapy. Symptoms may occur as early as 1 week following therapy initiation [51].
- b) Monitor elderly patients closely during therapy initiation [51].
- c) If abrupt discontinuation of therapy or rapid dose reduction is required, monitor patient for seizure precipitation, seizure exacerbation, or [status epilepticus](#); a gradual withdrawal is recommended.

4.2j Patient Instructions

Aj) [Clonazepam](#) (By mouth)

[Clonazepam](#)

Treats seizures, [panic disorder](#), and anxiety.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use this medicine if you had an [allergic reaction](#) to [clonazepam](#) or to similar medicines, are pregnant or breastfeeding, or have severe liver disease or [narrow-angle glaucoma](#).

How to Use This Medicine:

Tablet, Dissolving Tablet

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

Disintegrating tablet: Dry your hands before you handle the tablet. Place the tablet on your tongue and let it dissolve.

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

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

Drugs and Foods to Avoid:

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

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

[Propantheline](#)

[Theophylline](#)

Medicine to treat [fungal infections](#)

Do not drink alcohol while you are using this medicine.

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

Warnings While Using This Medicine:

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 have [kidney disease](#), liver disease, [glaucoma](#), or lung problems. Tell your doctor if you have a history of drug or [alcohol addiction](#), depression, or mental illness.

This medicine can increase thoughts of suicide. Tell your doctor right away if you start to feel depressed and have thoughts about hurting yourself. Report any unusual thoughts or behaviors that trouble you, especially if they are new or getting worse quickly.

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

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

This drug has a higher risk of overdose. Call your doctor if you have extreme dizziness or weakness, a slow heartbeat, or problems with coordination or memory.

This medicine may make you dizzy or drowsy. Do not drive, use machines, or do anything else that could be dangerous until you know how this medicine affects you.

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

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

Possible Side Effects While Using This Medicine:

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

[Allergic reaction](#): Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

Confusion, problems with coordination or memory

Depression, irritability, restlessness

Extreme tiredness or weakness, slow heartbeat, trouble breathing or speaking

Seizure, tremors

Unusual behavior or thoughts of hurting yourself

Worsening seizures

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

Drowsiness, tiredness

Fever, chills, [cough](#), sore throat, and body aches

Increased saliva

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

4.3] Place In Therapy

A) Seizure Disorder

1) [Clonazepam](#) is indicated alone or as adjunct therapy in the treatment of [Lennox-Gastaut syndrome](#) ([petit mal variant](#)), akinetic and [myoclonic seizures](#). A loss of anticonvulsant activity sometimes occurring within 3 months of administration may be reversed by dosage adjustments [51].

2) [Clonazepam](#) has been useful in treating absence seizures in patients refractory to conventional therapy. [Clonazepam](#) has also been effective in controlling sensory-precipitated [epilepsy](#) such as photomyoclonic or

"reading" epilepsy. Partial complex seizures and focal seizures do not respond as well to clonazepam as to other drugs.

3) Although clonazepam may be as effective as diazepam in treating status epilepticus, the drug's usefulness is limited by its cardiorespiratory depressant effects.

B) Panic Disorder

1) Clonazepam is indicated for the treatment of panic disorder, with or without agoraphobia. Efficacy for long-term use, greater than 9 weeks duration had not been studied. Therefore, patients should be periodically reassessed when clonazepam is used for extended periods of time [51].

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Chemically, clonazepam is 5 (2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-1, 4-benzodiazepin-2-one, a benzodiazepine derivative. It is believed that clonazepam's ability to exert an antiseizure and antipanic effect is related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system [233].

2) The anticonvulsant activity of clonazepam in much smaller doses is similar to that of diazepam and trimethadione. After oral and intravenous administration to humans, clonazepam has been found to be 5 to 10 times more effective as an anticonvulsant than diazepam [243]. Experimental studies with cats administered clonazepam intravenously showed that clonazepam had a longer lasting anti-convulsant action than diazepam (Canger, 1971).

B) REVIEW ARTICLES

1) The pitfalls of clonazepam discontinuation have been summarized [244].

2) The treatment and prophylaxis of facial neuralgias have been reviewed [245].

4.5] Therapeutic Uses

4.5.A] Benzodiazepine withdrawal, Alprazolam

1) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

May be useful for treating alprazolam withdrawal

3) Adult:

a) General Information

1j) Certain characteristics of [clonazepam](#) make it an appropriate choice for treating [alprazolam](#) withdrawal: (1) Cross-tolerance exist between benzodiazepines; (2) Benzodiazepines with longer half-lives are associated with withdrawal symptoms that are less severe and occur later than those associated with benzodiazepines with shorter half-lives [47]; (3) [Clonazepam](#) and [alprazolam](#) have similar binding affinities for the central-type benzodiazepine receptors; and (4) [Clonazepam's](#) anticonvulsant properties help protect against withdrawal seizure [48].

bj) Alprazolam-dependent patients (n=10) were withdrawn, with [clonazepam](#) being substituted in an equivalent amount to that of [alprazolam](#). [Clonazepam](#) was tapered by a mean daily dose of 1.17 mg. Withdrawal was successfully completed in 7 days [48].

cj) One patient was withdrawn from [alprazolam](#) dependence by adding 10 mg of [clonazepam](#) and tapering [alprazolam](#) from a dose of 26 mg. After the discontinuation of [alprazolam](#), [clonazepam](#) was then tapered by 1 mg/day. Withdrawal was completed without incidence [49].

dj) Patients with [panic disorder](#) (n=41) were switched from [alprazolam](#) to [clonazepam](#) using a 2:1 mg ([alprazolam:clonazepam](#)) equivalency. The switch over from [alprazolam](#) to [clonazepam](#) was completed without difficulty in 7 days [50].

4.5.Bj Burning mouth syndrome

1j) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2j) Summary:

Preliminary evidence suggests initial benefit in up to 70%, with a high discontinuation rate

3j) Adult:

aj) An open-label pilot study (n=30) found that [clonazepam](#) at an average daily dose of 1 mg produced some relief in 70% of subjects with burning mouth syndrome of unknown etiology. However, 38% of those who experienced improvement had to discontinue [clonazepam](#) because of adverse effects. The mechanism of action is unclear; placebo-controlled trials are needed [2].

4.5.Cj Depression

1j) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2) Summary:

Efficacy shown only in a small study and case reports

May be useful as short-term adjunct when initiating [fluoxetine](#) therapy

3) Adult:

a) [Clonazepam](#) 1.5 to 6 mg daily (mean, 3.4 mg/day) was reported effective in the treatment of depression in a controlled study involving 25 evaluable patients [3]. Marked-to-moderate improvement of depressive symptoms was observed in 21 patients (84%), with antidepressant effects generally occurring within 1 week of initiation of treatment. Side effects occurred in 12 patients during therapy, but the description of these effects was not provided. Similar results were reported in a case [4]. It is speculated that [clonazepam](#) produces antidepressant effects secondary to reduced utilization of serotonin, or decreased serotonin receptor sensitivity, via the [gamma-aminobutyric acid \(GABA\)](#) system [3].

b) When added to [fluoxetine](#), [clonazepam](#) 0.5 to 1 mg at bedtime demonstrated superior efficacy over [fluoxetine](#) alone when initiating therapy for moderate to marked depression in a double-blind, nonrandomized trial (n=80). Patients received adjunctive [clonazepam](#) or placebo for the first 21 days, followed by a gradual 12-day taper and discontinuation. The Hamilton depression rating scores were significantly more improved on days 7, 10 and 21 with combination therapy as compared with [fluoxetine](#) monotherapy. The percentage of responders based on 3 different depression rating scales was statistically significantly higher with [clonazepam](#) augmentation at all time points except day 42. Adverse events did not differ significantly between groups. Investigators reported a mild and transient worsening of symptoms after [clonazepam](#) discontinuation, possibly due to withdrawal syndrome or unmasking of [fluoxetine](#) side effects. They conclude that short-term [clonazepam](#) may be beneficial while awaiting the onset of [fluoxetine's](#) antidepressant effect [5].

4.5.D) Dystonia

1) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

2) Summary:

Benzodiazepines offer the best medical treatment for [hemidystonia](#).

3) Adult:

a) Among medical treatments tried for [hemidystonia](#), [clonazepam](#) and [diazepam](#) provided the best results, with 50% of patients showing some degree of improvement. Anticholinergics were effective in 30% of trials, and antiepileptic medications in 23%. These observations resulted from the analysis of records of 33 cases from one treatment center and 158 cases from the medical literature since 1966 [6].

4.5.E] Essential tremor**1) Overview**

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

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

2) Summary:

In a placebo-controlled study, [clonazepam](#) in oral doses up to 4 mg daily was ineffective in the treatment of benign essential tremor [7].

4.5.F] Mania**1) Overview**

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2) Summary:

Decreases manic symptoms in acutely manic patients

3) Adult:

a) In 2 controlled trials (Edwards et al, 1991) [8] and several case reports (Adler, 1986) [9]; (Greenspan & Levin, 1985) [10], [clonazepam](#) has been shown to decrease manic symptoms in acutely manic patients. Conflicting results have been obtained with respect to treatment of patients with [bipolar disorder](#) without psychotic symptomatology. No [relapses](#) were reported during a 13- to 34-month observation period in 6 patients treated with oral [clonazepam](#) 1.5 to 8 mg/day [11]; however, these sustained results were not been achieved in another study [12]. The mechanism by which [clonazepam](#) controls mania has not been determined. The main side effect is sedation, which may contribute to the beneficial effects seen. Large controlled trials are needed to determine the role of [clonazepam](#) in the acute and chronic treatment of mania.

4.5.G] Migraine; Prophylaxis

See Drug Consult reference: MIGRAINE -- RECOMMENDATIONS FOR PROPHYLAXIS IN ADULTS

4.5.H] Neuroleptic-induced acute akathisia**1) Overview**

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2) Summary:

Effective in case reports only

3) Adult:

a) In an open trial, [akathisia](#) disappeared in 17 patients, improved moderately in 3, and improved slightly in 1 patient following the addition of oral [clonazepam](#) 0.5 to 3 mg/day. All patients had been receiving oral neuroleptics for at least 3 months and had developed severe [akathisia](#). The neuroleptic-induced [akathisia](#) was not affected by antiparkinsonian drugs. The onset of effect with [clonazepam](#) was observed within 2 days. Only 3 patients reported adverse effects (drowsiness in 2 patients and increasing salivary excretion 1 patient) [1].

b) Addition of oral [clonazepam](#) 0.5 mg/day resulted in improvement in the [akathisia](#) score in 10 patients with neuroleptic-induced [akathisia](#). Patients had received oral neuroleptics and [benztropine](#) (2 to 4 mg/day) for at least 2 weeks. Subjectively, all patients reported improvement (Kutcher et al, 1987).

c) Neuroleptic-induced [akathisia](#) was successfully treated with a combination of [baclofen](#) and [clonazepam](#) in a case report. A 61-year-old man experienced severe [akathisia](#) 4 weeks after starting [haloperidol](#) 15 mg/day. Despite discontinuation of [haloperidol](#), the [akathisia](#) continued and was not affected by [carbidopa](#), [diazepam](#), trihexyphenidyl, or [orphenadrine](#). Within 48 hours after receiving oral [baclofen](#) 5 mg 3 times daily and [clonazepam](#) 0.5 mg 3 times daily, the [akathisia](#) markedly improved. The [baclofen](#) dose was increased to 10 mg 3 times a day and all restlessness abated. Subsequent attempts to decrease the dose of both drugs caused recurrence of the [akathisia](#) (Sandyk, 1985).

4.5.I] Panic disorder

FDA Labeled Indication

1) Overview

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

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

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

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

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

2) Summary:

[Clonazepam](#) is indicated for the treatment of adults with [panic disorder](#), with or without [agoraphobia](#) (as defined in DSM-IV) [15].

3) Adult:

a) **Clonazepam** was effective in the treatment of **panic disorder** with or without **agoraphobia** in a large multicenter trial. During a 6-week therapeutic phase, patients received either **clonazepam** (n=222) or placebo (n=216). **Clonazepam** was initiated at 0.25 mg/day and titrated to a maximum of 4 mg. This dose was maintained for the last 3 weeks. At the end of the titration, the mean **clonazepam** dose was 2.3 mg/day. At the therapeutic endpoint, 61.9% of **clonazepam** patients were panic-free compared with 36.8% of placebo patients (p less than 0.001). Panic attacks were reduced from 4.2 at baseline to 1.5 in the **clonazepam** group and 3.9 to 2.2 in the placebo group (p=0.004). During a 7-week discontinuation phase, **clonazepam** was slowly tapered to discontinuation. The **clonazepam** group showed a greater increase in the mean number of panic attacks at discontinuance (0.9 to 2.7) than the placebo group (1.5 to 1.8). However, the proportion of patients having more panic attacks at discontinuance than at baseline was similar in the 2 groups. Thus no rebound effect was apparent. **Clonazepam** appeared to be well tolerated throughout the study [16].

b) **Clonazepam** was efficacious in treating **panic disorder** in 10 patients. The mean number of panic attacks per week prior to treatment was 22.3 as compared with 8.44 after 4 weeks of treatment with **clonazepam** 1 to 3 mg daily. In addition, reductions were noted on the self-rating agoraphobic anxiety scale and agoraphobic avoidance scales. No significant effects were noted on the Zung self-rating Anxiety scale or the Zung Depression Scale. Minor side effects included increased irritability, short periods of loss of coordination and slight depression; no patient was significantly sedated [17]. Following 5 weeks of treatment, a statistically significant reduction in anxiety was noted following carbon dioxide challenge in this same group of patients [18].

c) **Clonazepam** 1.5 mg daily has been used in the treatment of panic attacks associated with **obsessive-compulsive disorder** in 1 case report. The patient had previously had a response to **lorazepam** treatment of his panic attacks, but obsessive-compulsive symptoms had not been ameliorated. **Clonazepam** was effective in reducing both constellations of symptoms [19].

4) Pediatric:

a) **Clonazepam** 0.5 mg twice daily was efficacious in the treatment of **panic disorder** in 4 adolescents. In addition to reductions in the frequency of panic attacks, levels of baseline anxiety as measured by the Hamilton Anxiety Rating Scale were significantly reduced over the 2-week study period [20].

b) **Clonazepam** 0.5 to 3 mg daily was used successfully in the treatment of severe anxiety disorders with panic-like symptoms in 3 prepubertal children (8 to 11 years of age) [21].

4.5.J] Restless legs syndrome

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:

Effective, in controlled studies and some case reports, for up to 3 months

3) Adult:

a) [Clonazepam](#) 0.5 to 2 mg at bedtime was reported effective in the treatment of periodic leg movements in sleep in a controlled study involving 20 patients. Significant decreases in the number of leg movements and improvement in sleep parameters were observed in clonazepam-treated patients, as compared with placebo, via polysomnographic recordings [22].

b) [Clonazepam](#) 1 mg orally at bedtime was reported effective in improving quality of sleep and leg dysesthesia in [restless legs syndrome](#) in a controlled study [23]. However, this study was only for a period of 7 days and longer studies are required.

c) [Clonazepam](#) 1 mg orally successfully treated [restless legs syndrome](#) in 4 siblings with [familial amyloid polyneuropathy](#) [24].

d) Symptomatic response to [clonazepam](#) was rapid and complete in 14 out of 15 patients with [renal failure](#) and treated for [restless legs syndrome](#). Most of the patients had been treated unsuccessfully with various sedatives and hypnotics, including other benzodiazepines [25].

4.5.K] Seizure

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; [Pediatric, yes \(up to 10 years or up to 30 kg\)](#)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

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

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

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

2) Summary:

[Clonazepam](#) is indicated as monotherapy or as adjunctive therapy in the treatment of [Lennox-Gastaut syndrome \(petit mal variant\)](#), akinetic and [myoclonic seizures](#), and may be useful in patients with absence seizures (petit mal) who have not responded to succinimides [15].

3) Adult:

a) Oral Administration

1) The antiepileptic effectiveness of [carbamazepine](#) and [clonazepam](#) were compared in 36 patients with newly diagnosed, untreated [psychomotor epilepsy](#). No significant differences in either decrease in seizure frequency or adverse effects were found between the 2 drugs during the 6-month treatment period [26].

2) Studies have shown that therapy with [clonazepam](#) often makes it possible to reduce or discontinue other [anticonvulsant therapy](#) [27] [28] [29] [30].

3) [Clonazepam](#) 1 mg twice daily in combination with [valproic acid](#) successfully controlled frontal lobe seizures in a 16-year-old girl hospitalized for [intractable epilepsy](#) due to supplementary motor seizures. Following a febrile illness at 6 months of age, the patient developed a seizure disorder that manifested as brief attacks of random tonic seizures. During the following 15.5 years, seizure frequency increased to 10 during both awake and sleep periods. Upon hospitalization, the patient was taking [carbamazepine](#) 400 mg 3 times daily

and vigabatrin 500 mg 3 times daily. During hospitalization, it was documented that the patient experienced 20 to 40 seizures while sleeping and 5 to 10 while awake. The seizure duration was 20 to 60 seconds followed by 4 to 5 minutes of [post-ictal confusion](#) that was sometimes associated with brief automatism. Following several EEGs and 3 MRIs, a diagnosis of supplementary motor seizures was made. A drug regimen of [lamotrigine](#) 50 mg twice daily titrated up to 100 mg twice daily was unsuccessful. At that time, [clonazepam](#) 0.5 mg twice daily was introduced and, upon titration to 1 mg twice daily, complete control of awake seizures and reduction of sleep seizures to 3 to 4 daily was achieved (Obeid, 1999).

4) [Clonazepam](#) has not proven effective in post-anoxic action myoclonus [31] but may be useful in [myoclonus epilepsy](#) and myoclonic movements with [dysarthria](#) [31] [32].

5) In case reports, [clonazepam](#) 0.5 to 1 mg 3 times daily has been shown to be effective in controlling [reading epilepsy](#), a rare variety of sensory-precipitated [epilepsy](#) [33] [34] [35].

6) [Clonazepam](#) suppresses photomyoclonic seizures [36] [37].

7) [Clonazepam](#) in combination with [phenobarbital](#) may be a useful prophylactic treatment in [leukemia](#) patients receiving [busulfan](#) and [cyclophosphamide](#) before [autologous bone marrow transplantation](#) [38].

b) Rectal Administration

1) Available data suggests that [clonazepam](#) is well absorbed rectally but that absorption may be erratic with considerable variability between individuals. [Clonazepam](#) (0.02 mg/kg) administered rectally as Rivotril(R) injection was absorbed rapidly, reaching peak concentrations in 10 to 30 minutes. Serum values after rectal administration were found to be comparable to the levels achieved after IV administration but relative bioavailability was not assessed (Klostervskov et al, 1983).

4) Pediatric:

a) Oral Administration

1) In 22 epileptic children (3 months to 20 years of age), refractory to conventional therapy, [clonazepam](#) was useful for childhood minor motor seizures and for refractory [petit mal seizures](#). Starting doses were 0.25 mg twice daily for children less than 6 years old and 0.5 mg twice daily for children older than 6, with an increase of 0.25 mg to 0.5 mg, every 3 to 4 days until seizures were controlled, or until side effects were observed. Six patients were completely controlled; 9 moderately (50% reduction of symptoms), and 9 experienced minimal results. Maintenance doses were up to 6.35 mg daily, and 15 patients had been treated with [clonazepam](#) for 6 months. Half of the patients responded to treatment in less than 3 weeks after initiation. Sixteen of the children were classified as having minor motor seizures and the others had a range of seizure types. Partial complex seizures and focal seizures did not respond as well to [clonazepam](#). Side effects of lethargy and ataxia occurred frequently. Four of the children had a mild elevation in SGOT levels and no accompanying abnormalities in liver function tests [39].

2) A 75% reduction in 7 of 10 children with [petit mal seizures](#) following [clonazepam](#) 0.05 to 0.3 mg/kg/day in divided doses for a period of 17 weeks was reported. One patient exhibited a 30% reduction in seizures [40].

3) Doses of 1 to 4 mg daily in divided doses were administered to infants with [epilepsy](#) not responding to previous therapy. Children in this study received 6 to 12 mg daily in divided doses. Good to excellent results were obtained in 10 of 21 patients treated [41].

4) Seizures were controlled in 11 of 20 patients (ages 2 to 51 years) with various types of intractable seizure disorders treated with [clonazepam](#). Best responses were observed in patients with previously uncontrolled [petit mal seizures](#) (Hooshmand (1972).

5) [Clonazepam](#) 0.5 to 2 mg daily was administered for infantile [epilepsy](#) unresponsive to other anticonvulsant agents [42].

b) Rectal Administration

1) Rectal anticonvulsants were used successfully as an alternative route to oral drug therapy in children with seizures who underwent [gastrointestinal surgery](#). Eight children with seizure disorders underwent [gastrostomy](#) placement and [Nissen fundoplication](#); all children were receiving oral anticonvulsants prior to surgery (various combinations of [clonazepam](#), [valproate](#), [diazepam](#), [phenobarbital](#), and [phenytoin](#)) but could not continue oral therapy before and after surgery. Perioperative rectal therapy was employed for [clonazepam](#), [diazepam](#), and [valproate](#) (retention enema in tap water or saline), and given until the patients could again receive oral medications. The duration of use was generally 48 to 72 hours. If the patient was taking [phenytoin](#) or [phenobarbital](#), these were given IV before and after surgery. All patients maintained excellent seizure control without toxicity from the rectally administered preparations [43].

2) Peak concentrations were observed between 10 minutes and 2 hours after [clonazepam](#) (as Rivotril(R) solution) was administered rectally to children (Ryalance et al, 1986).

4.5.L) [Sleep walking disorder](#)

1) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2) Summary:

May be effective in the treatment of [somnambulism](#) or sleepwalking

3) Adult:

a) [Diazepam](#) has been successfully used to treat [somnambulism](#) or sleepwalking. However, there are cases in which benzodiazepines acted to cause [somnambulism](#) when used to treat insomnia. Standard therapy with [diazepam](#) or [clonazepam](#) is preferred for [somnambulism](#). There is a need for well-controlled studies involving [somnambulism](#) patients treated with [diazepam](#) in order to correctly evaluate the efficacy of treatment.

b) [Clonazepam](#) was effective in a study in which patients were admitted due to a variety of sleep disorders. One hundred patients were studied over a 6-year period of time. Fifty-four of the 100 patients suffered from night terrors and sleepwalking; this included complex and/or vigorous behaviors appearing during abrupt arousals from non-REM sleep. Injury had resulted from [somnambulism](#) in many cases, which was the reason these patients were involved in the study. [Clonazepam](#) 0.25 to 2 mg at bedtime was prescribed for 51.9% (28 of 54 patients) of the patients with the most vigorous or dangerous nocturnal behaviors. Rapid and sustained control was achieved up to 6 years in 83.6% of the patients treated with [clonazepam](#). The authors concluded that [clonazepam](#) proved to be effective and lasting for the patients in this study. They also recommended a holiday from the drug therapy to determine the necessity for continued treatment [45].

c) A patient who experienced [somnambulism](#) was successfully treated with [clonazepam](#). A 57-year-old man developed increasingly agitated [somnambulism](#) that occurred 1 to 7 nights a week. Other medications were unsuccessful in controlling this behavior. He was treated with 0.5 mg of [clonazepam](#) at bedtime, which controlled [somnambulism](#) for a 9-month follow-up period. The authors concluded that the use of [clonazepam](#) is indicated in controlling various types of motor disorders of sleep. The authors preferred [clonazepam](#) due to its safety and rapid, lasting efficacy [46].

d) [Clonazepam](#) therapy was effective in a case involving [somnambulism](#). A 52-year-old woman with diagnosed [paranoid schizophrenia](#) for 16 years was taking 350 mg per day of [chlorpromazine](#) and 55 mg IM [fluphenazine](#) every 2 weeks. The patient started to complain of sleepwalking and continued to somnambulate several times a week. A change in her neuroleptic to IM [haloperidol](#) 300 mg every 2 weeks was not beneficial. Five years after the events began, [clonazepam](#) 0.5 mg at bedtime was prescribed due to increasingly dangerous sleepwalking episodes. One month later, the frequency of [somnambulism](#) had decreased. The [clonazepam](#) dose was increased to 2.5 mg at bedtime and all episodes were eliminated for several months. The author concluded that [clonazepam](#) is clinically effective in the treatment of [somnambulism](#) (Goldboom & Chouinard, 1984).

4.5.M] [Social phobia](#)

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:

Effective for up to 11 months of therapy based on uncontrolled data

3) Adult:

a) Results of a 6-month open-label study (n=56) of [clonazepam](#) 1 to 2.5 mg daily followed by double-blind randomization (n=36) to 5 months of continued therapy (CT) versus discontinuation therapy (DT) via slow taper suggest efficacy for [social phobia](#). The initial treatment phase resulted in significant improvements in the Clinical Global Impressions Scale, Brief [Social Phobia](#) Scale, and Marks-Sheehan Main Phobia Severity Scale for Fear and Avoidance. While no patients on CT relapsed, 21% of subjects who underwent a slow taper over 6 to 18 weeks relapsed (p=not significant). Some scale values

were significantly worse at certain timepoints in the DT group as compared with the CT group. No significant between-group differences occurred with respect to withdrawal symptoms. Subjects in the CT group did not deteriorate clinically after a rapid (3-week) taper at the end of the trial [44].

4.5.N] Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Alprazolam

4.6.A.1] Panic disorder

a) Alprazolam in doses of up to 10 milligrams daily was reported as effective as clonazepam (up to 5 mg daily) in the treatment of panic attacks in a placebo-controlled study involving 44 patients (18 to 65 years of age) [248].

4.6.B] Carbamazepine

4.6.B.1] Psychomotor epilepsy

a) Clonazepam and carbamazepine were equally effective in the treatment of newly diagnosed and previously untreated psychomotor epilepsy. In a double-blind, randomized study, 36 patients were maintained on either clonazepam 6 milligrams/day or carbamazepine 900 milligrams/day for a period of 6 months. Plasma levels for each drug remained within the therapeutic range throughout treatment. Both drugs were equally effective in controlling epilepsy. Side effects were similar for both drugs [251].

4.6.C] Clobazam

1) Adverse Effects

a) Clobazam was less sedating than clonazepam in a double-blind, placebo-controlled, crossover study with 10 healthy volunteers [247]. The doses were those recommended as starting doses for patients with epilepsy: clobazam 10 to 20 milligrams and clonazepam 0.5 to 1 milligram. While clonazepam significantly affected sedation, psychomotor response, and postural sway, clobazam did not reach statistical significance (p less than 0.05) in any of the tests when compared with placebo.

4.6.D] Cyclobenzaprine Hydrochloride

4.6.D.1] Temporomandibular joint disorder

a) Cyclobenzaprine was superior to placebo and to clonazepam for reducing jaw pain on awakening. In a randomized, double-blind, placebo-controlled trial, 41 patients diagnosed with TMD of myofascial origin were given clonazepam 0.5 milligrams (mg), placebo, or cyclobenzaprine 10 mg daily for 3 weeks, in addition to education about TMD and a self-care regimen. Jaw pain upon awakening was significantly reduced by all 3 treatments ($p=0.0007$, $p=0.0003$, and $p=0.001$, respectively). However, improvement was significantly greater with cyclobenzaprine than with placebo (p less than 0.004) or clonazepam (p less than 0.004). Efficacy of clonazepam was not different from that of placebo. None of the treatments had a significant effect on sleep quality, which was poor in a majority of subjects. Side effects of morning drowsiness, dry mouth, and nightmares were reported by 62% of subjects receiving cyclobenzaprine; morning drowsiness and headaches by 40% of those receiving clonazepam; and drowsiness, dry mouth, and an increase in premenstrual symptoms in 20% of those receiving placebo [252].

4.6.E] Diazepam

4.6.E.1] Status epilepticus

a) Intravenous (IV) [clonazepam](#) was administered to 17 children (2 weeks to 15 years of age) in [status epilepticus](#) [258]. The initial [clonazepam](#) dose was 0.25 milligram as a bolus injection; this dose was repeated at 30-second intervals until the seizures stopped. Intravenous [diazepam](#) was used for comparison in 6 children who had further episodes of [status epilepticus](#). [Clonazepam](#) was as effective as [diazepam](#) in halting seizure activity (all 17 episodes of status were successfully stopped within 3 minutes by intravenous (IV) [clonazepam](#)) and had a longer mean duration of action ([clonazepam](#): 24.5 hours versus [diazepam](#) 8.8 hours). Although reported side effects in this study were minimal, one worker feels that [clonazepam's](#) use in status will be limited by its cardiorespiratory depressant effects [259]. There is no IV [clonazepam](#) preparation currently available.

4.6.F] Ethosuximide

4.6.F.1] Absence seizure

a) [Clonazepam](#) is effective for the treatment of absence seizures, but generally less so than [ethosuximide](#) [257].

4.6.G] Haloperidol

4.6.G.1] Gilles de la Tourette's syndrome

a) In a retrospective study, [haloperidol](#), [clonazepam](#), and [clonidine](#) were compared in the treatment of 81 patients suffering multifocal tic disorders, either [Tourette's syndrome](#) or chronic motor tics. The most effective drug for treating [Tourette's syndrome](#) was [haloperidol](#), mean dose of 5.8 milligrams/day. The most effective drug for treating chronic motor tics was [clonazepam](#), mean dose of 4.8 milligrams/day. [Clonidine](#) was effective in six patients, but only in combination with either [haloperidol](#) or [clonazepam](#). The authors recommend treatment with [clonazepam](#) first, due to the risk of [tardive dyskinesia](#) associated with [haloperidol](#). Then [clonazepam](#) in combination with [clonidine](#), if [clonazepam](#) alone is not effective. Then in nonresponsive patients [haloperidol](#) should be used [253].

4.6.G.2] Psychotic disorder

a) [Clonazepam](#) and [haloperidol](#) (both given by the intramuscular route) were compared for tranquilization of agitated psychotic patients with manic symptoms. Fifteen patients received three doses of either [clonazepam](#) 1 to 2 milligrams or [haloperidol](#) 5 to 10 milligrams at 30 minute intervals. Both drugs successfully controlled the agitation, but [haloperidol](#) gave a more rapid response [254]. Better results may have been obtained by administering single higher doses of intramuscular (IM) [clonazepam](#): 4 to 5 milligrams of IM [clonazepam](#) every 30 to 60 minutes seems to be effective, safe and rapid for the control of acute psychotic agitation and onset of action may be similar to IM [haloperidol](#) (Benazzi & Mazzoli, 1994).

4.6.H] Imipramine

4.6.H.1] Panic disorder

a) Preliminary results from an ongoing double blind study comparing [imipramine](#) and [clonazepam](#) in the treatment of [panic disorders](#) in twelve patients have been reported [249]. Six patients received [imipramine](#) and six received [clonazepam](#), and all were treated for a total of six months. [Clonazepam](#) treated patients required an average of 1.6 mg/day (range 1 to 3 mg/day) to achieve relief of symptoms; [imipramine](#) patients

required 62.5 mg/day) (range 25 to 75 mg/day). During the final four months of the study no patients required more than 2 mg/day of [clonazepam](#) or 50 mg/day of [imipramine](#). Over the course of the first two weeks of treatment a substantial drop in the incidence of panic attacks occurred in both groups. Mean scores in global improvement were significantly improved in both groups, as were patients assessed scores and physician assessed scores. These early results demonstrate the efficacy of both [imipramine](#) and [clonazepam](#) in the control of [panic disorders](#).

4.6.I] [Lorazepam](#)

4.6.I.1] [Mania](#)

a) [Lorazepam](#) was superior to [clonazepam](#) in treating acute mania in 21 patients in a well designed study. A significant improvement in mood, [logorrhea](#), insight, grandiosity, hostility, and excitement was observed in 11 patients receiving [lorazepam](#) 12.5 milligrams (mean) in 3 divided doses compared to 10 patients treated with [clonazepam](#) 12.75 milligrams (mean) in 3 divided doses. By day 14, 61.5% of the lorazepam-treated patients responded to treatment, with 38.5% of patients achieving remission, compared with a 18.2% response rate and a 0% remission rate with [clonazepam](#). Following 14 days of monotherapy, [lithium](#) was added to the regimen and 4 patients in the clonazepam-treated group achieved remission along with 3 additional patients in the lorazepam-treated group on day 28 [255].

4.6.I.2] [Status epilepticus](#)

a) Intravenous [lorazepam](#) was compared with [clonazepam](#) in 61 patients with [status epilepticus](#). [Lorazepam](#) alone 4 to 10 milligrams, [clonazepam](#) 1 milligram, alone or both [lorazepam](#) and [clonazepam](#) at different times were administered to a total of 61 patients in [status epilepticus](#). In comparing the overall EEG and clinical results, [lorazepam](#) produced greater EEG improvement, while [clonazepam](#) provided a greater improvement in clinical symptoms. The only adverse effect associated with [lorazepam](#) administration was a change in the degree of alertness, persisting up to 24 hours. Drowsiness after [clonazepam](#) therapy was brief, persisting only 3 to 4 hours. However, 4 clonazepam-treated patients developed respiratory difficulties [256].

4.6.J] [Propranolol](#)

4.6.J.1] [Parkinsonian tremor](#)

a) Long-acting [propranolol](#) (160 milligrams daily) was reported superior to [primidone](#) (250 milligrams daily) and [clonazepam](#) (4 milligrams daily) in the treatment of parkinsonian tremor in a double-blind, crossover study involving 10 patients [250].

4.6.K] [Sertraline Hydrochloride](#)

4.6.K.1] [Social phobia](#), Refractory

a) In a 12-week randomized trial of patients with generalized [social anxiety disorder](#) who remained symptomatic (Leibowitz Social Anxiety Scale (LSAS) score greater than 50) despite 10 weeks of initial [sertraline](#) monotherapy (N=181), treatment with [clonazepam](#) in addition to continued [sertraline](#) was associated a significantly higher response rate (LSAS score 50 or lower) of 56% and a significant decrease in the mean LSAS score (mean 26.5 point reduction) compared with continued [sertraline](#) plus placebo (a 36% response rate and mean LSAS point reduction of 16.5). In comparison, treatment with [venlafaxine](#) resulted in a response rate of 46% and a mean 17.6 point reduction in LSAS scores; neither outcome was significantly different from continued treatment with either [sertraline](#) plus placebo or [sertraline](#) plus [clonazepam](#). Remission rates (LSAS score 30 or lower) between all 3 treatment groups were not

significantly different (27%, [sertraline](#) plus [clonazepam](#); 17% [sertraline](#) plus placebo; 19%, [venlafaxine](#)). Somnolence was more frequent among patients in the [sertraline](#) plus [clonazepam](#) group (32%) compared with the [venlafaxine](#) (15%) and [sertraline](#) plus placebo groups (23%) [246].

4.6.L] [Venlafaxine Hydrochloride](#)

4.6.L.1] [Social phobia](#), Refractory

a) In a 12-week randomized trial of patients with generalized [social anxiety disorder](#) who remained symptomatic (Leibowitz Social Anxiety Scale (LSAS) score greater than 50) despite 10 weeks of initial [sertraline](#) monotherapy (N=181), treatment with [clonazepam](#) in addition to continued [sertraline](#) was associated a significantly higher response rate (LSAS score 50 or lower) of 56% and a significant decrease in the mean LSAS score (mean 26.5 point reduction) compared with continued [sertraline](#) plus placebo (a 36% response rate and mean LSAS point reduction of 16.5). In comparison, treatment with [venlafaxine](#) resulted in a response rate of 46% and a mean 17.6 point reduction in LSAS scores; neither outcome was significantly different from continued treatment with either [sertraline](#) plus placebo or [sertraline](#) plus [clonazepam](#). Remission rates (LSAS score 30 or lower) between all 3 treatment groups were not significantly different (27%, [sertraline](#) plus [clonazepam](#); 17% [sertraline](#) plus placebo; 19%, [venlafaxine](#)). Somnolence was more frequent among patients in the [sertraline](#) plus [clonazepam](#) group (32%) compared with the [venlafaxine](#) (15%) and [sertraline](#) plus placebo groups (23%) [246].

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