

DRUGDEX-EV 0657

MICROMEDEX

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ALPRAZOLAM

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

0.0] Overview

1] Class

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

Antianxiety

2] Dosing Information

a) Adult

1] Anxiety

a) immediate-release or orally disintegrating tablet, 0.25 to 0.5 mg ORALLY 3 times a day, may increase every 3 to 4 days if necessary; MAX daily dose, 4 mg in divided doses [1] [2]

2] [Panic disorder](#), With or without [agoraphobia](#)

a) immediate-release or orally disintegrating tablets, 0.5 mg ORALLY 3 times a day; may increase dosage by up to 1 mg/day every 3 to 4 days; usual dosage range, 1 to 10 mg/day (mean, 5 to 6 mg/day) [1] [2]

b) extended-release, 0.5 to 1 mg ORALLY once daily in the morning, may increase dosage by up to 1 mg/day every 3 to 4 days; usual dosage range is 3 to 6 mg/day [27]

3] Contraindications

a) hypersensitivity to benzodiazepines [57] [58] [59] [60]

b) [narrow angle glaucoma](#), acute [57] [58] [59] [60]

c) concomitant use with [ketoconazole](#) or [itraconazole](#) [57] [58] [59] [60]

4] Serious Adverse Effects

a) Drug withdrawal seizure

b)) [Liver failure](#)

c)) [Stevens-Johnson syndrome](#)

5)) Clinical Applications

a)) FDA Approved Indications

1)) Anxiety

2)) [Panic disorder](#), With or without [agoraphobia](#)

1.0) Dosing Information

[Drug Properties](#)

[Storage and Stability](#)

[Adult 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

[Alprazolam](#)

C)) Physicochemical Properties

1)) Molecular Weight

a)) 308.76 [57] [58]

2)) Solubility

a)) Insoluble in water (at physiological pH), but soluble in alcohol [60] [59], methanol, and ethanol [57] [58]

1.2) Storage and Stability

A)) Oral route

1)) Solution/Tablet/Tablet, Disintegrating/Tablet, Extended Release

a)) Store immediate-release and orally disintegrating tablets at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F) with excursions for orally disintegrating tablets allowed between 15 and 30 degrees C (59 and 86 degrees F); protect orally disintegrating tablets from moisture [57] [60].

b)) Store extended-release tablets at controlled room temperature, 25 degrees C (77 degrees F); excursions permitted to 15 to 30 degrees C (59 to 86 degrees F) [58].

c)) Store oral solution at a controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F) and protect from light. Discard opened bottle after 90 days [59].

B)) Extemporaneous Formulation - Oral route

1)) An [alprazolam](#) oral liquid 1 milligram/milliliter (mg/mL) may be compounded using either a 1:1 mixture of Ora-Sweet and Ora-Plus (Paddock Laboratories), a 1:1 mixture of Ora-Sweet SF and Ora-Plus (Paddock Laboratories), or cherry syrup concentrate diluted 1:4 with simple syrup (Robinson Laboratory, Inc) as vehicles [447]. Sixty [alprazolam](#) 2-mg tablets are comminuted in a mortar to a fine powder. Approximately 40 mL of the vehicle is added and mixed into a fine paste. The vehicle should be added in geometric portions almost to volume and mixed thoroughly after each addition. Transfer the contents to a calibrated bottle and add enough vehicle to bring the final volume to 120 mL. The bottle may be labeled: shake well before using, protect from light, and expires in 60 days. The solution was found to retain a mean of at least 91% of the initial drug concentration for 60 days stored at 5 or 25 degrees Celsius in the dark. The vials used were amber clear polyethylene terephthalate prescription ovals with low-density polyethylene foam cap linings.

1.3] Adult Dosage**1.3.1] Normal Dosage****1.3.1.A] [Alcohol withdrawal syndrome](#)**

1)) The mean optimal oral daily dose of [alprazolam](#) in the treatment of chronic withdrawal from alcohol was reported to be 2.2 milligrams daily [26].

1.3.1.B] [Anxiety](#)

1)) The recommended initial dose of [alprazolam](#) for anxiety is immediate-release tablets (including orally disintegrating tablets) 0.25 to 0.5 milligram three times daily. The dose may be titrated up every 3 to 4 days to a maximum dose of 4 milligrams daily . The lowest effective dose should be used [15] [16].

2)) Effective doses in the treatment of anxiety are 0.5 to 4 milligrams daily in divided doses [8] [6] [17].

1.3.1.C] [Depression](#)

1)) Average daily doses that have been shown effective in the treatment of depression are 2.5 to 3 milligrams daily in divided doses [20] [19] [17].

1.3.1.D] [Panic disorder](#), With or without [agoraphobia](#)**1)) IMMEDIATE-RELEASE TABLETS**

a)) The recommended initial dose of [alprazolam](#) immediate-release tablets (including orally disintegrating tablets) for the treatment of [panic disorders](#) is 0.5 milligrams (mg) 3 times daily . The dose may be increased by up to 1 mg every 3 to 4 days. A slower titration may be needed at doses greater than 4 mg/day. The medication should be divided into 3 or 4 doses evenly distributed throughout the day. A dosage range of 1 to 10 mg daily has been used with mean doses of 5 to 6 mg daily [15] [16].

b)) A reduction in panic attacks has occurred with [alprazolam](#) 2 milligrams/day, but higher doses of 6 milligrams/day increase the likelihood of being panic-free. Careful, individualized [alprazolam](#) dose adjustments are needed to achieve the desired treatment response while minimizing undesirable side effects (Lesser et al, 1992).

2)) EXTENDED-RELEASE TABLETS

a)) Do not break, chew or crush extended-release tablets.

b) The recommended initial dose of [alprazolam](#) extended-release tablets is 0.5 to 1 milligram (mg) once daily. The dose may be increased by up to 1 mg every 3 to 4 days. A slower titration may be necessary to allow full expression of the pharmacodynamic effect. A dosage range of 3 to 6 mg daily has been used, however, some patients may require a dose as high as 10 mg daily [33].

1.3.1.E) WITHDRAWAL SCHEDULE

1) When discontinuing therapy the daily dose should be decreased by 0.5 milligrams every 3 days [15] [33] [16].

1.3.1.F) IMMEDIATE TO EXTENDED-RELEASE TABLET SWITCH

1) Patients currently receiving divided doses of [alprazolam](#) immediate-release tablets may be switched to [alprazolam](#) extended-release tablets at the same total daily dose taken once daily [33].

1.3.1.G) ORALLY DISINTEGRATING TABLETS - PATIENT INSTRUCTIONS

1) [Alprazolam](#) orally disintegrating tablets should be removed from the bottle with dry hands just before administration and placed immediately on top of the tongue to disintegrate; swallow with saliva. If only half of a tablet is used, the unused portion of the tablet should be discarded, as it may not remain stable. Discard any cotton that was included in the bottle and reseal tightly to prevent introducing moisture which may cause the tablets to disintegrate [15].

1.3.3] Dosage in [Hepatic Insufficiency](#)

A) IMMEDIATE-RELEASE TABLETS

1) The recommended initial dose of [alprazolam](#) immediate-release tablets (including orally disintegrating tablets) in patients with advanced liver disease is 0.25 milligram (mg) given 2 or 3 times daily [15] [16]. The dose may be gradually increased as needed and as tolerated.

B) EXTENDED-RELEASE TABLETS

1) The recommended initial dose of [alprazolam](#) extended-release tablets in patients with advanced liver disease is 0.5 milligrams (mg) once daily. The dose may be gradually increased as needed and tolerated [33].

C) BENZODIAZEPINES

1) Among the class as a whole, [LORAZEPAM](#), [OXAZEPAM](#), and [TEMAZEPAM](#) may be the benzodiazepines of choice for patients with liver disease. These 3 agents undergo glucuronide conjugation and their half-lives are only slightly altered in the presence of [hepatic dysfunction](#). Other benzodiazepines may be used, but the dosage or dosing interval may need to be altered to compensate for impaired hepatic metabolism [47] [48] [49] [50] [51] [52].

1.3.4] Dosage in Geriatric Patients

A) IMMEDIATE-RELEASE TABLETS

1) The elimination half-life of [alprazolam](#) has been demonstrated to be prolonged in elderly men, but not women. Dosing adjustments are suggested in elderly men [53].

2) [Alprazolam](#) in initial doses of 0.5 milligrams orally twice a day, increasing by 0.5 milligrams daily every 3 days to a maximum of 4 milligrams daily, was effective in 12 of 18 elderly patients (age 56 to 78) with depression. Initial drowsiness was the only side effect observed [54].

3)) In elderly patients, the recommended initial dose of [alprazolam](#) immediate release tablets (including orally disintegrating tablets) is 0.25 milligrams administered two to three times a day, and titrated as tolerated [15] [16]. If adverse effects occur with the starting dose, the dose should be lowered.

B)) EXTENDED-RELEASE TABLETS

1)) The recommended initial dose of [alprazolam](#) extended-release tablets in elderly patients is 0.5 milligrams (mg) once daily. The dose may be gradually increased as needed and tolerated [33].

1.3.6] Dosage in Other Disease States

A)) OBESITY

1)) In obese patients, [alprazolam](#) will require a longer time to reach steady-state concentrations when given long-term, as compared to normal subjects. However, final steady-state levels achieved will be similar to concentrations observed in patients with normal body weight, assuming that [alprazolam](#) doses are adjusted to ideal rather than body weight [55]

B)) PATIENTS WITH DEBILITATING DISEASE

1)) IMMEDIATE-RELEASE TABLETS

a)) The recommended initial dose of [alprazolam](#) immediate-release tablets (including orally disintegrating tablets) in patients with a debilitating disease is 0.25 milligram (mg) given 2 or 3 times daily [15] [16]. The dose may be gradually increased as needed and as tolerated.

2)) EXTENDED-RELEASE TABLETS

a)) The recommended initial dose of [alprazolam](#) extended-release tablets in patients with debilitating disease is 0.5 milligrams (mg) once daily. The dose may be gradually increased as needed and tolerated [33].

2.0] Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1] Onset and Duration

A)) Onset

1)) Initial Response

a)) Anxiety, oral (immediate release): 1 to 1.5 hours [294]

1)) A single dose of oral alprazolam reduces anxiety within 1 to 1.5 hours [294].

2.2] Drug Concentration Levels

A)) Therapeutic Drug Concentration

1)) Anxiety: 20 to 40 mcg/L [294]

a)) Although a therapeutic concentration range is not clearly established, some studies indicate that optimal reduction of anxiety associated with [panic disorder](#) occurs at steady-state plasma [alprazolam](#) concentrations of 20 to 40 mcg/L. Concentrations higher than this may be needed for suppression of the actual panic attacks [294].

B) Peak Concentration

1) Oral, 0.5 to 3 mg: 8 to 37 nanograms/mL [63] [57] [60]

a)) Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3 mg, peak levels of 8 to 37 nanograms/mL are observed, regardless of dosage form administered [63] [57] [60].

b)) Peak plasma levels are approximately 15% higher in Asians compared with Caucasians [63] [57] [60].

c)) Plasma concentrations of [alprazolam](#) may be reduced by as much as 50% in cigarette smokers compared with non-smokers [63] [57] [60].

d)) Diurnal variation was observed when evaluating the C_{max} of extended-release [alprazolam](#). When dosed at night, the C_{max} increased by 30% compared with morning dosing [63].

2) Sublingual, 1 mg: 17.3 nanograms/mL [299]

a)) The mean C_{max} after a single fasted dose of 1 mg taken sublingually (17.3 +/- 1.2 nanograms/mL) was not significantly different from the mean C_{max} after a single fasted dose of 1 mg taken orally (14.4 +/- 1.4 nanograms/mL) when studied in a [pharmacokinetic study](#) in 13 healthy men and women [299].

C) Time to Peak Concentration

1) Oral, disintegrating tablet: 1.5 to 2.5 hr [57] [295]

a)) C_{max} is reached about 1.5 to 2 hours after an orally disintegrating tablet is administered with or without water. When taken with water, the mean T_{max} occurs 15 minutes earlier than when taken without water [57].

b)) Mean peak plasma levels of 16.13 nanograms/mL at 2.5 hours (median, 0.75 to 4.01 hours) were achieved following a single fasted dose of a 1 mg orally disintegrating tablet when evaluated in a [pharmacokinetic study](#) in 16 healthy men and women [295].

2) Oral, extended-release tablet: 5 to 11 hours [63] [296]

a)) Extended-release [alprazolam](#) tablets have a slower rate of absorption compared with immediate release tablets. Peak plasma concentrations occur between 5 and 11 hours after dosing [63].

b)) The C_{max} occurred 9.4 to 11 hours after administration of an extended-release tablet in a single-dose [pharmacokinetic study](#) in 24 healthy men [296].

c)) Diurnal variation was observed when evaluating the absorption rate of extended-release [alprazolam](#). When dosed at night, the T_{max} decreased by 1 hour compared with morning dosing [63].

3) Oral, immediate release tablet: 1 to 2 hours [60]

a) Peak plasma concentrations occur within 1 to 2 hours following oral administration [60].

4) Sublingual tablet: 1.17 hours [299]

a) The mean Tmax after a single fasted dose of 1 mg taken sublingually (1.17 +/- 0.25 hr) was not significantly different from the mean Tmax after a single fasted dose of 1 mg taken orally (1.73 +/- 0.28 hr) when evaluated in a [pharmacokinetic study](#) in 13 healthy men and women [299].

D) Area Under the Curve

1) Oral, disintegrating tablet, single-dose, 1 mg: 256.9 nanograms x hr/mL [295]

a) Following administration of a single dose of 1 mg orally disintegrating tablet in a [pharmacokinetic study](#) in healthy men and women (n=16) in an overnight 10-hour fasted state, the AUC (from zero to infinity) was 256.9 +/- 96.13 nanograms x hr/mL [295].

2) Oral, extended-release tablet, single-dose, 2 mg: 428 to 460 nanograms x hr/mL [296]

a) Using an extended-release tablet, the AUC normalized to a 2-mg dose, was 428 to 460 nanograms x hr/mL in a single-dose [pharmacokinetic study](#) in 24 healthy men [296].

3) Oral, immediate release tablet, single-dose, 1 mg: 249 nanograms x hr/mL [297].

a) Following oral administration of a single dose of 1 mg in a [pharmacokinetic study](#) in 16 healthy adults, the AUC was 249 nanograms x hr/mL [297].

b) Systemic exposure to [alprazolam](#) is greater in cirrhotic patients (529 nanograms x hr/mL) [298].

4) Sublingual, immediate release tablet, single-dose, 1 mg: 203.7 nanograms x hr/mL [299]

a) The mean AUC after a single fasted dose of 1 mg taken sublingually (203.7 +/- 15.7 nanograms x hr/mL) was not significantly different from the mean AUC after a single fasted dose of 1 mg taken orally (194.4 +/- 17.8 nanograms x hr/mL) when evaluated in a [pharmacokinetic study](#) in 13 healthy men and women [299].

2.3] ADME

2.3.1] Absorption

A) Bioavailability

1) Oral: readily absorbed [60] [57] [63]

a) Following oral administration, [alprazolam](#) is readily absorbed from the gastrointestinal tract [60] [57] [63]

2) Oral, extended-release tablets: 90% [63].

- a) The mean absolute bioavailability of the extended-release tablets is approximately 90%, which is comparable to bioavailability of the immediate-release tablets [63].

B) Effects of Food

1) Oral, disintegrating tablet: decreased Cmax 25% and increased Tmax by 1.5 hours [295]

- a) The median Tmax increased when a single dose of 1 mg orally disintegrating tablet was given after a high-fat meal (4 hours, range 2.53 to 6.03 hours) compared with the median Tmax after a single fasted dose of 1 mg orally disintegrating tablet (2.5 hours, range 0.75 to 4.01 hours) when evaluated in a [pharmacokinetic study](#) in 16 healthy men and women. The mean Cmax decreased by approximately 25% during fed conditions (12.43 nanograms/mL) when compared with fasted conditions (16.13 nanograms/mL); although, the AUC (extrapolated to infinity) was not significantly different [295].

2) Oral, extended-release tablet: increased Cmax 25% and variable effects on Tmax [63]

- a) Mean Cmax increased by approximately 25% when extended-release [alprazolam](#) is given within 2 hours of a high-fat meal. Eating a high-fat meal immediately before dosing reduced Tmax by about 1/3; however, increase of Tmax by about 1/3 occurred when a high-fat meal is consumed 1 hour or more after dosing. Overall systemic exposure (AUC) is not effected by eating [63].

2.3.2] Distribution

A) Distribution Sites

1) Protein Binding

- a) 80%, majority to albumin [63] [60] [57] [300].

1) Alprazolam is 80% bound to serum proteins, with the majority being to albumin [63] [60] [57] [300].

2) Plasma protein binding is unchanged in obese subjects compared with normal subjects [301].

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Liver, extensive via CYP3A4 [63] [60] [57]

- a) [Alprazolam](#) is metabolized via hydroxylation, catalyzed by CYP3A4 [63] [60] [57].

B) Metabolites

1) 4-hydroxy-alprazolam: minimally active [63] [60] [57]

- a) The plasma concentrations of 4-hydroxy-alprazolam and alpha-hydroxy-alprazolam increased proportionally with dose; although the combined plasma concentration of the

metabolites was less than 15% of unchanged concentrations of [alprazolam](#) for all doses (2 mg, 4 g, 8 mg, and 10 mg) in a [pharmacokinetic study](#) of extended-release [alprazolam](#) in 24 healthy adults [296].

b)) Relative potency based on benzodiazepine receptor binding is 20% that of [alprazolam](#); and due to low plasma concentrations relative to unchanged [alprazolam](#), this major metabolite is unlikely to contribute to pharmacological effects [63] [60] [57].

2)) Alpha-hydroxy-alprazolam: minimally active [63] [60] [57]

a)) The plasma concentrations of 4-hydroxy-alprazolam and alpha-hydroxy-alprazolam increased proportionally with dose; although the combined plasma concentration of the metabolites was less than 15% of unchanged concentrations of [alprazolam](#) for all doses (2 mg, 4 g, 8 mg, and 10 mg) in a [pharmacokinetic study](#) of extended-release [alprazolam](#) in 24 healthy adults [296].

b)) Biological activity is approximately two-thirds that of [alprazolam](#); however, because of low plasma concentrations relative to unchanged [alprazolam](#), this major metabolite is unlikely to contribute to pharmacological effects [63] [60] [57].

2.3.4] Excretion

A)) Kidney

1)) Renal Clearance (rate)

a)) 371 mL/hr [302].

1)) The renal clearance of alprazolam was 371 mL/hr [302].

2)) Renal clearance is significantly decreased in elderly men [300].

2)) Renal Excretion (%)

a)) 80% [303]

1)) Approximately 80% of an alprazolam dose is excreted renally, as unchanged drug and metabolites [303] [63] [60] [57].

B)) Feces

1)) 7% [303] [302]

a)) Approximately 7% of an [alprazolam](#) dose is excreted in the feces [303] [302].

C)) Total Body Clearance

1)) 76 mL/minute [297].

a) Total clearance following oral [alprazolam](#) was 76 mL/min, and was similar in both groups when evaluated in a [pharmacokinetic study](#) of 16 subjects (young (mean age 29.8 years), n=8; elderly (mean age 68.4 years), n=8) [297].

2.3.5] Elimination Half-life

A) Parent Compound

1) 10.6 to 12.5 hours, normal subjects; 16.3 hr, elderly subjects; 19.7 hr, liver disease; 21.8 hr, obese subjects [63] [60] [57] [299] [304] [301].

a) The mean elimination half-life of [alprazolam](#) after oral administration of the immediate release tablet to healthy adults is 11.2 hours (range, 6.3 to 26.9 hr) [60].

b) The mean elimination half-life after a single fasted dose of a 1 mg immediate release tablet taken sublingually (11.7 +/- 1.2 hr) was not significantly different from the mean elimination half-life after a single fasted dose of 1 mg taken orally (11.8 +/- 1.6 hr) when evaluated in a [pharmacokinetic study](#) in 13 healthy men and women [299].

c) The mean elimination half-life of [alprazolam](#) after administration of the oral disintegrating tablet to healthy adults is 12.5 hours (range, 7.9 to 19.2 hours) [57].

d) The mean elimination half-life of [alprazolam](#) following oral administration of the extended-release tablet to healthy adults ranges from 10.7 to 15.8 hours [63].

e) A mean elimination half-life of 11 hours was reported in normal adult subjects (range, 6.3 to 15.8 hr; n=16) compared with 16.3 hours in healthy elderly subjects (range 9 to 26.9 hr; n=16) [63] [60] [57] [304] [298]

f) A mean elimination half-life of 11.4 hours was reported in healthy adults (range, 6.3 to 26.9 hr; n=17) compared with 19.7 hours in patients with [alcoholic liver disease](#) (range 5.8 to 65.3 hr; n=17) [63] [60] [57] [298]

g) A mean elimination half-life of 10.6 hours was observed in healthy adults (range, 6.3 to 15.8 hr; n=12) compared with 21.8 hours in obese patients (range 9.9 to 40.4 hr; n=12) [63] [60] [57] [301].

h) Elimination half-life is approximately 25% higher in Asians compared with Caucasians [63] [57] [60].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

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

[Drug Interactions](#)

3.1] Contraindications

A) hypersensitivity to benzodiazepines [57] [58] [59] [60]

- B) [narrow angle glaucoma](#), acute [57] [58] [59] [60]
C) concomitant use with [ketoconazole](#) or [itraconazole](#) [57] [58] [59] [60]

3.2] Precautions

- A) abrupt dose reduction or discontinuation; increased risk of withdrawal symptoms including life-threatening seizures; gradual dose reduction recommended [57] [58] [59] [60]
B) alcohol or drug abuse, history; increased risk of drug abuse and dependence; monitoring recommended [57] [58] [59] [60]
C) [alcoholic liver disease](#) or [obesity](#); increased systemic exposure may occur [57] [58] [59] [60]
D) concomitant use with potent CYP3A inhibitors not recommended [57] [58] [59] [60]
E) depression; increased risk of [hypomania](#) and mania and may increase suicidality [57] [58] [59] [60]
F) elderly or debilitated patients; increased risk of ataxia or oversedation; dose adjustment recommended [57] [58] [59] [60]
G) [hepatic disease](#), advanced; increased systemic exposure may occur; dose adjustment recommended [57] [58] [59] [60]
H) physical and psychological dependence may occur; increased risk with dose greater than 4 mg/day or longer duration of use [57] [58] [59] [60]
I) pregnancy; may increase risk for [birth defects](#) in newborns when used during first trimester; avoid use during first trimester [57] [58] [59] [60]
J) [pulmonary disease](#), severe; increased risk of adverse events, including rare fatalities [57] [58] [59] [60]
K) seizures, history or current; increased risk for recurrence with rapid discontinuation; slow taper recommended [57] [58] [59] [60]
L) suicidality, history or current; increased risk [57] [58] [59] [60]
M) withdrawal symptoms, including life-threatening seizures, have occurred following dose reduction, missed doses, and discontinuation [57] [58] [59] [60]
N) report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Chest pain

- 1) During premarketing evaluation, chest pain was reported in 1% or more patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3.3.1.B] Hypotension

- 1) Incidence: immediate-release, 4.7%; extended-release, 0.1% to less than 1% [63] [57] [64] [59]
2) During premarketing evaluation, hypotension was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].
3) In clinical studies of patients with anxiety disorder, hypotension occurred in 4.7% of patients treated with [alprazolam](#) (n=565) over 4 weeks in dosages up to 4 mg/day compared with 2.2% of patients treated with placebo (n=505) [57] [64] [59].

3.3.1.C] Palpitations

- 1) During premarketing evaluation, palpitation was reported in at least 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3.3.1.D] Peripheral edema

1) Peripheral edema has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].

3.3.2] Dermatologic Effects

3.3.2.A] Photosensitivity

1) A report of photosensitivity due to [alprazolam](#) in a 41- year-old man was made. The patient presented with a 2-day history of itching, redness and scaling over the face following a single dose of 1 milligram (mg) of [alprazolam](#), taken the day prior to appearance of the symptoms. He mentioned a similar episode 1 month prior also after ingestion of [alprazolam](#). The rash resolved with topical corticosteroid treatment, and the patient was advised to use photoprotection. After resolution, a challenge was done with 0.5 mg of [alprazolam](#) and within 12 hours the rash appeared in the same areas [76].

2) A 65-year-old-man suffered a pruritic erythematous rash on sun-exposed areas after 1 month of [alprazolam](#) 0.4 mg 3 times daily. An oral photo-challenge test with UVA radiation was positive while a photopatch test was negative [77].

3.3.2.B] Rash

1) Incidence: immediate-release, 10.8%; extended-release, 0.1% to less than 1% [63] [57] [64] [59]

2) During premarketing evaluation, rash was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), rash occurred in 10.8% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 8.1% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.2.C] Stevens-Johnson syndrome

1) [Stevens-Johnson syndrome](#) has been reported with [alprazolam](#) therapy during postmarketing surveillance [63] [57] [64] [59].

3.3.3] Endocrine/Metabolic Effects

3.3.3.A] Decrease in appetite

1) Incidence: 7.3% to 27.8% [63] [57] [64] [59]

2) In clinical studies of patients with [panic disorder](#), decreased appetite occurred in 7.3% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 7.2% of patients treated with placebo (n=349) [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), decreased appetite occurred in 27.8% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 24.1% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.3.B] Gynecomastia

1) [Gynecomastia](#) has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].

3.3.3.C] Hyperprolactinemia

1) [Hyperprolactinemia](#) has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].

3.3.3.D] Increased appetite

1) Incidence: 7% to 32.7% [63] [57] [64] [59]

2) In clinical studies of patients with [panic disorder](#), increased appetite occurred in 7% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 6% of patients treated with placebo (n=349) [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), increased appetite occurred in 32.7% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 22.8% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.3.E] Weight decreased

1) Incidence: 4.3% to 22.6% [59] [64] [57] [59]

2) In clinical studies of patients with [panic disorder](#), decreased weight occurred in 4.3% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 3.7% of patients treated with placebo (n=349) [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), weight loss occurred in 22.6% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 16.5% of patients treated with placebo (n=1231). Weight loss led to treatment discontinuation in 13.3% of patients (n=641) in clinical studies with [alprazolam](#) for [panic disorder](#) [57] [64] [59].

3.3.3.F] Weight increased

1) Incidence: 2.7% to 27.2% [59] [64] [57]

2) In clinical studies of patients with [panic disorder](#), increased weight occurred in 5.1% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 4.3% of patients treated with placebo (n=349) [63].

3) In clinical studies of patients with anxiety disorder, weight gain occurred in 2.7% of patients treated with [alprazolam](#) (n=565) over 4 weeks in dosages up to 4 mg/day compared with 2.7% of patients treated with placebo (n=505) [57] [64] [59].

4) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), weight gain occurred in 27.2% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 17.9% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.4] Gastrointestinal Effects

3.3.4.A] Constipation

1) Incidence: 8.1% to 26.2% [63] [64] [59] [57]

2) In clinical studies of patients with [panic disorder](#), constipation occurred in 8.1% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 4.3% of patients treated with placebo (n=349) [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), constipation occurred in 26.2% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 15.4% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.4.B] Drug-induced gastrointestinal disturbance

1J) **Gastrointestinal disorders** have been reported during postmarketing surveillance of **alprazolam** [61] [62].

3.3.4.C] **Excessive salivation**

1J) Incidence: 4.2% to 5.6% [57] [64] [59]

2J) In clinical studies of patients with anxiety disorder, increased salivation occurred in 4.2% of patients treated with **alprazolam** (n=565) over 4 weeks in dosages up to 4 mg/day compared with 2.4% of patients treated with placebo (n=505) [57] [64] [59].

3J) In clinical studies of patients with **panic disorder** with or without **agoraphobia**, increased salivation occurred in 5.6% of patients treated with **alprazolam** (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 4.4% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.4.D] **Gastroesophageal reflux disease, Nocturnal**

1J) An increase in nocturnal **acid reflux** was reported in 3 of 10 patients receiving **alprazolam** 0.25 mg every 8 hours [74].

3.3.4.E] **Nausea**

1J) Incidence: 6% [63]

2J) In clinical studies of patients with **panic disorder**, nausea occurred in 6% of patients treated with extended-release **alprazolam** (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 3.2% of patients treated with placebo (n=349) [63].

3.3.4.F] **Reduced salivation**

1J) Incidence: 32.8% [57] [64] [59]

2J) In clinical studies of patients with **panic disorder** with or without **agoraphobia**, decreased salivation occurred in 32.8% of patients treated with **alprazolam** (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 34.2% of patients treated with placebo (n=1231). Decreased salivation led to treatment discontinuation in 10.6% of patients (n=641) in clinical studies with **alprazolam** therapy for **panic disorder** [57] [64] [59].

3.3.4.G] **Taste sense altered**

1J) Taste alterations have been reported [74].

3.3.4.H] **Xerostomia**

1J) Incidence: 10.2% to 14.7% [63] [57] [64] [59]

2J) In clinical studies of patients with **panic disorder**, dry mouth occurred in 10.2% of patients treated with extended-release **alprazolam** (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 9.7% of patients treated with placebo (n=349) [63].

3J) In clinical studies of patients with anxiety disorder, dry mouth occurred in 14.7% of patients treated with **alprazolam** (n=565) over 4 weeks in dosages up to 4 mg/day compared with 13.3% of patients treated with placebo (n=505) [57] [64] [59].

3.3.6] **Hepatic Effects**

3.3.6.A] **Hepatitis**

1J) [Hepatitis](#) has been reported with [alprazolam](#) therapy in postmarketing experience, although a causal relationship could not be determined [63] [64] [57] [59].

3.3.6.B] Increased liver enzymes

1J) Liver enzyme elevation has been reported with [alprazolam](#) therapy during postmarketing surveillance [63] [64] [57] [59].

3.3.6.C] Liver failure

1J) [Hepatic failure](#) has been reported with [alprazolam](#) therapy in postmarketing experience, although a causal relationship could not be determined [63] [64] [57] [59].

3.3.8] Musculoskeletal Effects

3.3.8.A] Arthralgia

1J) Incidence: 2.4% [63]

2J) In clinical studies of patients with [panic disorder](#), arthralgia occurred in 2.4% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 0.6% of patients treated with placebo (n=349) [63].

3.3.9] Neurologic Effects

3.3.9.A] Ataxia

1J) Incidence: 7.2% [63]

2J) In clinical studies of patients with [panic disorder](#), ataxia occurred in 7.2% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 3.2% of patients treated with placebo (n=349) [63].

3.3.9.B] Cognitive disorder

1J) Incidence: 28.8% [57] [64] [59]

2J) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), [cognitive disorder](#) occurred in 28.8% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 20.5% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.9.C] Confusion

1J) Incidence: 1.5% to 10.4% [63] [57] [64] [59]

2J) In clinical studies of patients with [panic disorder](#), confusion occurred in 1.5% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 0.9% of patients treated with placebo (n=349) [63].

3J) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), confusional state occurred in 10.4% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 8.2% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.9.D] Delirium

1J) [Delirium](#) has been reported in association with [alprazolam](#) withdrawal [69]; (Zipursky et al, 1985).

2) **Delirium** was described during withdrawal of **alprazolam** in a 68-year-old male that was unresponsive to **diazepam** administration (40 mg over 14 hours). **Delirium** resolved after reinstitution of **alprazolam** (Zipursky et al, 1985).

3.3.9.E] Drug withdrawal seizure

1) Seizures and **status epilepticus** have occurred following **alprazolam** discontinuation or reduction of dosages greater than 4 mg/day for 4 to 22 weeks in 8 patients treated for **panic disorder** in clinical trials (n=1989). Five cases occurred following abrupt discontinuation or reduction in dosages ranging from 2 to 10 mg/day. Seizure occurred following a single 1 mg dose after tapering from **alprazolam** 6 mg/day at a rate of 1 mg/day every 3 days. Other voluntary reports have noted seizures during gradual drug tapering. Seizure risk appears highest 24 to 72 hours after **alprazolam** discontinuation [63] [57] [64] [59].

2) Withdrawal seizures have been reported with rapid or abrupt discontinuation of **alprazolam**. Seizures and other withdrawal symptoms have been reported following even brief **alprazolam** therapy at recommended dosages for anxiety ranging from 0.75 mg to 4 mg/day. Dosages above 4 mg/day or long-term treatment (more than 12 weeks) may increase the risk of withdrawal seizures. CNS depressants should not be abruptly withdrawn, especially in patients with a history of **epilepsy** or seizures. Gradual dosage tapering of no more than 0.5 mg every 3 days under close supervision is recommended [63] [57] [64] [59].

3) **Myoclonic seizures** have been reported following abrupt withdrawal from **phenelzine** and **alprazolam** [70]. Withdrawal symptomatology occurs within 72 hours of abstinence. Seizures were self-limiting and of short duration, and the total daily dosage of **alprazolam** exceeded the manufacturer's recommended maximum daily dose of 4 mg for 8 weeks to 18 months in these cases [71]. Grand mal seizure has been associated with discontinuation of **alprazolam** [72] [69] [73].

3.3.9.F] Dysarthria

1) Incidence: 10.9% to 23.3% [63] [57] [64] [59]

2) In clinical studies of patients with **panic disorder**, **dysarthria** occurred in 10.9% of patients treated with extended-release **alprazolam** (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 2.6% of patients treated with placebo (n=349), including discontinuation of treatment in 2.1% and 0% of extended release **alprazolam** and placebo patients, respectively [63].

3) In clinical studies of patients with **panic disorder** with or without **agoraphobia**, **dysarthria** occurred in 23.3% of patients treated with **alprazolam** (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 6.3% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.9.G] Headache

1) Incidence: 1% or greater [63]

2) During premarketing surveillance of **alprazolam**, headache was reported in 1% or more patients receiving extended-release **alprazolam** for **panic disorder** (n=531) [63]f.

3.3.9.H] Incoordination

1) Incidence: 9.4% to 40.1% [63] [57] [64] [59]

2) In clinical studies of patients with **panic disorder**, abnormal coordination occurred in 9.4% of patients treated with extended-release **alprazolam** (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 0.9% of patients treated with placebo (n=349), including discontinuation of treatment in 1.9% and 0.3% of extended release **alprazolam** and placebo patients, respectively [63].

3) In clinical studies of patients with **panic disorder** with or without **agoraphobia**, impaired coordination occurred in 40.1% of patients treated with **alprazolam** (n=1388) up to 10 weeks in dosages of up to 10

mg/day (average dosage, 5 to 6 mg/day) compared with 17.9% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.9.I] Insomnia

1) Incidence: 1% or greater [63]

2) During premarketing surveillance of [alprazolam](#), insomnia was reported in 1% or more patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3.3.9.J] Lightheadedness

1) Incidence: 20.8% [57] [64] [59]

2) In clinical studies of patients with anxiety disorder, lightheadedness occurred in 20.8% of patients treated with [alprazolam](#) (n=565) over 4 weeks in dosages up to 4 mg/day compared with 19.3% of patients treated with placebo (n=505) [57] [64] [59].

3.3.9.K] Memory impairment

1) Incidence: 15.4% to 33.1% [63] [57] [64] [59]

2) In clinical studies of patients with [panic disorder](#), [memory impairment](#) occurred in 15.4% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 6.9% of patients treated with placebo (n=349), including discontinuation of treatment in 1.5% and 0.3% of extended release [alprazolam](#) and placebo patients, respectively [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), [memory impairment](#) occurred in 33.1% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 22.1% of patients treated with placebo (n=1231) [57] [64] [59].

4) After 8 weeks of [alprazolam](#) therapy in [panic disorder](#) patients, marked impairments were noted on word recall tasks. Patients were still impaired at the 24-week medication-free follow-up as compared to placebo patients. Patients were again tested 3.5 years later and found that the impairments did not persist [66].

5) The benzodiazepines do not affect the memory or events that have occurred prior to taking the drug. Benzodiazepines produce impairments in attention and vigilance. They do not appear to affect the storage capacity of short-term memory. They produce a dose-dependent anterograde impairment in the acquisition of newly learned information. Amnesia and sedation produced by the benzodiazepines are clearly related, yet are distinct phenomena. The amnesic effects of [alprazolam](#) are consistent with that of benzodiazepines as a group [67].

6) In a test of learning performance consisting of the ability to recall 16 words, the [alprazolam](#) (9.8 +/- 1.2) group differed significantly from placebo (14.3 +/- 0.7) at 24 hours after a single oral dose (Greenblatt et al, 1988).

3.3.9.L] Paresthesia

1) Incidence: 2.4% [63]

2) In clinical studies of patients with [panic disorder](#), paresthesia occurred in 2.4% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 1.7% of patients treated with placebo (n=349) [63].

3.3.9.M] Sedated

1) Incidence: 45.2% [63]

2) In clinical studies of patients with [panic disorder](#), sedation occurred in 45.2% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 22.6% of patients treated with placebo (n=349), including discontinuation of treatment in 7.5% and 0.6% of extended release [alprazolam](#) and placebo patients, respectively [63].

3) In a large double-blind multicenter study involving 526 patients with [agoraphobia with panic attacks](#) or [panic disorder](#), the most frequent side effect observed with [alprazolam](#) (1 to 10 mg daily) was sedation, occurring in 62%, 48% and 38% of patients after the 1st, 4th, and 8th week of treatment, respectively [68].

4) The side effects of [alprazolam](#) were reported in a multicenter study involving 525 patients with [agoraphobia with panic attacks](#) or [panic disorder](#). In this study, [alprazolam](#) was given in dosages of 1 to 10 mg daily for 8 weeks (mean, 4.9 and 5.7 mg daily at weeks 4 and 8, respectively). The most frequent side effects of [alprazolam](#) were sedation, ataxia, fatigue, slurred speech, amnesia and increased appetite; all these side effects tended to subside over the 8-week treatment period. The most frequent side effect was sedation, occurring in 60% of patients after the first week of treatment; the incidence declined thereafter to 48% and 38% at weeks 4 and 8, respectively [68].

3.3.9.N] Somnolence

1) Incidence: 23% to 76.8% [63] [57] [64] [59]

2) In clinical studies of patients with [panic disorder](#), somnolence occurred in 23% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 6% of patients treated with placebo (n=349), including discontinuation of treatment in 3.2% and 0.3% of extended release [alprazolam](#) and placebo patients, respectively [63].

3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), drowsiness occurred in 76.8% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 42.7% of patients treated with placebo (n=1231) [57] [64] [59].

4) In clinical studies of patients with anxiety disorder, drowsiness occurred in 41% of patients treated with [alprazolam](#) (n=565) over 4 weeks in dosages up to 4 mg/day compared with 21.6% of patients treated with placebo (n=505) [57] [64] [59].

5) Drowsiness with [alprazolam](#) was reported to occur less frequently than with [diazepam](#) in 1 study. These effects are generally observed at the beginning of therapy and will subside with continued therapy [65].

3.3.9.O] Tremor

1) Incidence: 0.1% to less than 1% [63]

2) During premarketing surveillance of [alprazolam](#), tremor was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3.3.10] Ophthalmic Effects

3.3.10.A] Blurred vision

1) Incidence: 1% or greater [63]

2) During premarketing evaluation, blurred vision was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].

3) In a summary of adverse reactions in 1,717 patients treated with [alprazolam](#), 7% reported blurred vision [75].

3.3.12] Psychiatric Effects

3.3.12.A] Aggressive behavior

1) Incidence: 0.1% to less than 1% [63].

- 2) During premarketing evaluation, aggression was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].
- 3) Combativeness has been reported following ingestion of 60 mg [alprazolam](#) by a 29-year-old female [78].
- 4) Dangerously aggressive behavior occurred in a 34-year-old man approximately 8 hours after he ingested about 10 mg [79].

3.3.12.B] Anxiety

- 1) Incidence: 1.1% [63]
- 2) In clinical studies of patients with [panic disorder](#), anxiety occurred in 1.1% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 0.6% of patients treated with placebo (n=349) [63].

3.3.12.C] Depression

- 1) Incidence: 12.1% [63]
- 2) In clinical studies of patients with [panic disorder](#), depression occurred in 12.1% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 9.2% of patients treated with placebo (n=349), including discontinuation of treatment in 2.5% and 1.2% of extended release [alprazolam](#) and placebo patients, respectively [63].

3.3.12.D] Hypomania

- 1) [Hypomania](#) has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].
- 2) Hypomanic episodes have been reported with [alprazolam](#) therapy in patients with depression [63] [57] [64] [59].

3.3.12.E] Irritability

- 1) Incidence: immediate-release, 33.1%; extended-release 1% or more [63] [57] [64] [59]
- 2) During premarketing evaluation, irritability was reported in 1% or more patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].
- 3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), irritability occurred in 33.1% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 30.1% of patients treated with placebo (n=1231). Irritability led to treatment discontinuation in 10.5% of patients (n=641) in clinical studies with [alprazolam](#) therapy for [panic disorder](#) [57] [64] [59].

3.3.12.F] Mania

- 1) Mania has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].
- 2) [Manic episodes](#) have been reported with [alprazolam](#) therapy in patients with depression [63] [57] [64] [59].
- 3) During premarketing evaluation, mania was reported in 0.1% to less than 1% of patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].
- 4) Mania occurred in 2 patients receiving [alprazolam](#) for [bipolar disorder](#). Symptoms occurred following therapy with 2.5 to 4 mg daily for 10 to 14 days. However, as the authors suggested, [bipolar disorders](#) can be characterized by the spontaneous occurrence of mania and a definite cause/effect relationship with [alprazolam](#) was not established in this report [80].
- 5) Manic symptoms were described in a 25-year-old woman with panic attacks during [alprazolam](#) therapy, which resolved following withdrawal of the drug and did not recur with substitution of [lorazepam](#). The patient received [alprazolam](#) 1.5 mg daily for approximately 3 weeks, with apparent improvement in panic

attacks and elevation in mood; at that time, the dosage was increased to 2 mg daily, resulting in manic symptoms within 48 hours. Dosage reduction to 0.75 mg daily resulted in resolution of manic symptoms within 2 days. Rechallenge with [alprazolam](#) again resulted in the occurrence of [manic behavior](#) when dosages exceeded 1.5 mg daily. Substitution of [alprazolam](#) with [lorazepam](#) (3 mg daily) did not produce recurrence of manic symptoms; the dosage was decreased to 2.5 mg daily due to excessive sedation, with no signs of [hypomania](#) or mania, and control of panic attacks. Manic symptoms developed in a 25-year-old male with no previous history of [bipolar disorder](#) while receiving 1.5 to 2 mg of [alprazolam](#)/day for [agoraphobia with panic attacks](#) [81].

3.3.13] Renal Effects

3.3.13.A] Difficulty passing urine

- 1) Incidence: 1% to 12.2% [63] [57] [64] [59]
- 2) During premarketing surveillance of [alprazolam](#), difficulty in micturition was reported 1% or more patients receiving extended-release [alprazolam](#) for [panic disorder](#) (n=531) [63].
- 3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), micturition difficulties occurred in 12.2% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 8.6% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.14] Reproductive Effects

3.3.14.A] Disorder of menstruation

- 1) Incidence: 3.5% to 10.4% [63] [57] [64] [59]
- 2) In clinical studies of patients with [panic disorder](#), [dysmenorrhea](#) occurred in 3.6% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 2.9% of patients treated with placebo (n=349) [63].
- 3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), [menstrual disorders](#) occurred in 10.4% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 8.7% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.14.B] Reduced libido

- 1) Incidence: 6% to 14.4% [63] [57] [64] [59]
- 2) In clinical studies of patients with [panic disorder](#), decreased libido occurred in 6% of patients treated with extended-release [alprazolam](#) (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 2.3% of patients treated with placebo (n=349) [63].
- 3) In clinical studies of patients with [panic disorder](#) with or without [agoraphobia](#), decreased libido occurred in 14.4% of patients treated with [alprazolam](#) (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 8% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.16] Other

3.3.16.A] [Angioedema](#)

- 1) [Angioedema](#) has been reported during postmarketing surveillance of [alprazolam](#) [61] [62].

3.3.16.B] Drug dependence

1) **Alprazolam** dependence may occur even with short-term use within recommended daily dosages (0.75 to 4 mg/day) for anxiety disorder and transient anxiety treatment. In controlled discontinuation studies, **alprazolam** discontinuation was successfully completed within 6 to 8 weeks in 71% to 93% of patients. Risk of physical and psychological dependence may increase with long-term treatment (more than 12 weeks), with dosages greater than 4 mg/day, or with a prior history of alcohol or drug abuse; however, evidence has revealed variations. In a controlled, postmarketing, discontinuation study in patients with **panic disorder** treated with dosages higher than 4 mg/day, there was no effect on the ability to taper to zero dose between patients treated for a 3-month duration compared with 6-month duration; however, patients who received greater than 4 mg/day had more difficulty tapering to zero dose than patients who received lower dosages. In randomized, placebo-controlled, discontinuation studies in **panic disorder** patients, rates of rebound or withdrawal symptoms were higher in **alprazolam** recipients than with placebo [63] [57] [64] [59]. Risk may be less with the extended release formulation than with the immediate release formulation [82].

2) Compared to extended-release (XR) **alprazolam**, equivalent doses of immediate-release (IR) **alprazolam** tended to produce greater effects on measures indicative of drug abuse liability. Fourteen male volunteers with histories of **polydrug abuse** were given in a randomized, double-blind, crossover manner the following: placebo, 1 and 2mg IR **alprazolam**, and 2 and 3 mg XR **alprazolam**. For equivalent doses, the following comparisons were noted: a) the XR formulation showed a lower maximal concentration and slower time to maximal concentration; b) subject-rated strength of drug effect was lower with XR **alprazolam**; c) the IR formulation tended to have more effects on behavioral performance measures; and d) IR **alprazolam** was more readily identified as a benzodiazepine by subjects [82].

3) According to the System to Retrieve Information from Drug Evidence (STRIDE) data compiled by the DEA, **diazepam** has the highest rate of illicit use with all other benzodiazepines having only negligible rates of abuse in comparison. **Alprazolam** and **lorazepam** were found to be more **diazepam**-like than **oxazepam**, **halazepam**, or **chlordiazepoxide** by some investigators. Frequency of abuse however, not only depends upon reinforcing/subjective/behavioral effects of the particular benzodiazepine, but upon local customs and fads, drug availability, and knowledge of the drug's actions [83].

4) Seven cases of **alprazolam** dependence were described. All patients were being treated for anxiety or depression, and developed dependence with dosages ranging from 2 to 12 mg daily for periods of 6 months to 3 years. Six patients abused other drugs or alcohol, either concurrently with **alprazolam** or in the past. Withdrawal symptoms occurred in all patients, including seizures, and 6 demonstrated tolerance to **alprazolam**. These data suggest that even small doses of **alprazolam** can result in dependence if used for long periods; patients with a history of dependence and addictive behavior are more likely to become dependent upon **alprazolam** [84].

3.3.16.C] Drug withdrawal

See Drug Consult reference: BENZODIAZEPINE-WITHDRAWAL SCHEDULE AND SYMPTOMS

3.3.16.D] Fatigue

1) Incidence: 13.9% to 48.6% [63] [57] [64] [59]

2) In clinical studies of patients with **panic disorder**, fatigue occurred in 13.9% of patients treated with extended-release **alprazolam** (n=531) for up to 8 weeks in dosages up to 10 mg/day compared with 9.2% of patients treated with placebo (n=349), including discontinuation of treatment in 1.7% and 0.6% of extended release **alprazolam** and placebo patients, respectively [63].

3) In clinical studies of patients with **panic disorder** with or without **agoraphobia**, fatigue and tiredness occurred in 48.6% of patients treated with **alprazolam** (n=1388) up to 10 weeks in dosages of up to 10 mg/day (average dosage, 5 to 6 mg/day) compared with 42.3% of patients treated with placebo (n=1231) [57] [64] [59].

3.3.16.E] Withdrawal sign or symptom

1) Summary

a) **Alprazolam** withdrawal symptoms have occurred even after brief therapy at recommended doses. Symptoms have ranged from insomnia, mild **dysphoria**, tremors and convulsions, vomiting, sweating, and abdominal and muscle cramps. Decreased appetite, weight loss, blurred vision, diarrhea, paresthesias, clouded sensorium, dysosmia, impaired concentration, and heightened sensory perception have also been observed. Rarely, patients with underlying psychiatric conditions, concomitant CNS drug use, or a history of drug or alcohol abuse have experienced hallucinations, aggressive or hostile behavior, irritability, rage, and agitation. Withdrawal seizures attributable to **alprazolam** have occurred with drug discontinuation or dose reduction. Risk of seizure seems to be greatest at 24 to 72 hours after discontinuation. Immediate management may require reinstitution of **alprazolam** at levels that suppress symptoms. [63] [57] [64] [59]. Multiple seizures and **status epilepticus** have also been reported [84] [72]. A case study reported the occurrence of severe **hypertension**, **sinus tachycardia**, and **bronchospasm** [85].

2) In a controlled clinical trial examining withdrawal symptoms with **alprazolam** discontinuation (n=63), decreased appetite, weight loss, blurred vision, diarrhea, muscle cramps or twitches, paresthesias, clouded sensorium, dysosmia, impaired concentration, and heightened sensory perception were observed. Anxiety and insomnia were also seen, but whether the cause was illness return, rebound, or withdrawal was unclear. Additional withdrawal symptoms reported were insomnia, mild **dysphoria**, tremors and convulsions, vomiting, sweating, and abdominal and muscle cramps. Withdrawal symptoms reported with **alprazolam** discontinuation in patients with **posttraumatic stress disorder** have included irritability, **intrusive thoughts**, and hostility. Immediate management may require reinstitution of **alprazolam** at dosages that suppress the symptoms. **Alprazolam** dependence can occur even with short-term use within the recommended 0.75 mg to 4 mg/day dosages for anxiety disorder and transient anxiety treatment. Postmarketing reports suggest that risk and severity appear greatest in patients on long-term therapy (more than 12 weeks) at dosages greater than 4 mg/day. Because **panic disorder** treatment often requires **alprazolam** dosages greater than 4 mg/day, these patients may have a higher risk of dependency. Randomized controlled studies of patients with **panic disorder** revealed high rates of rebound and withdrawal symptoms in alprazolam-treated patients compared with placebo. **Alprazolam** discontinuation was successfully completed within 6 to 8 weeks in 71% to 93% of patients compared with 89% to 96% of placebo-treated patients during controlled discontinuation studies. Treatment duration of 3 months compared with 6 months had no effect on the ability of **panic disorder** patients to taper to zero dose in controlled postmarketing discontinuation studies [63] [57] [64].

3) Withdrawal seizures attributable to **alprazolam** have occurred with drug discontinuation or dose reduction. Risk of seizure seems to be greatest at 24 to 72 hours after discontinuation. Multiple seizures and **status epilepticus** have also been reported [63] [57] [64] [59] [84] [72].

4) Patients (n=50) with **panic disorder** taking either **alprazolam**, **diazepam** or placebo for 8 months were asked to stop taking these medications at a relatively rapid rate of dose reduction. It was found that the majority of patients relapsed. Typical benzodiazepine withdrawal syndrome was identified. Perhaps the most distinctive were the unusual or distorted perceptions. These included a feeling of movement when there was none and the perception that body parts had become separated from the rest of the body. Also reported were sensations of floating and falling, shimmering vision, and faulty depth perception. Those who were taking **alprazolam** showed earlier and more intense rebound anxiety and withdrawal symptoms than did the patients who received **diazepam** [86].

5) Complete reversal of withdrawal symptoms was observed within hours of reinstitution of **alprazolam**. The effects of **alprazolam** withdrawal were evaluated in patients with **panic disorder** and phobic avoidance who had received the drug in dosages of 2 to 10 mg orally daily for 8 weeks. **Alprazolam** was discontinued

over a period of 4 weeks with follow-up continuing for a further 2 weeks. Significant [relapse](#) occurred between the first and last week of tapering, as compared to no [relapses](#) occurring with patients treated with placebo who also underwent tapering. However, during the second week following withdrawal, outcome scores were similar in each group. A rebound of panic attacks occurred in 27% of patients treated with [alprazolam](#) during tapering. A distinct withdrawal syndrome was observed in 35% of patients treated with [alprazolam](#) (eg, confusion, clouded sensorium, dysosmia, muscle cramps, blurred vision), whereas no withdrawal symptoms were observed in placebo-treated patients. Symptom rebound and a withdrawal syndrome occurring simultaneously was observed in 10% of patients treated with [alprazolam](#), and subsided by the end of the second week without [alprazolam](#). It is recommended that treatment of patients with [panic disorder](#) be for a longer period (6 months) and that the drug be discontinued more gradually, at least over an 8-week period [87].

6) A paranoid syndrome has been described as a complication of gradual [alprazolam](#) withdrawal [88].

7) A case of [delirium](#) during withdrawal of [alprazolam](#) was described in a 68-year-old male that was unresponsive to [diazepam](#) administration (40 mg over 14 hours). [Delirium](#) resolved after reinstitution of [alprazolam](#) (Zipursky et al, 1985).

8) [Delirium](#) and seizures were reported secondary to the abrupt withdrawal of [alprazolam](#) in a 77-year-old man [69].

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: Unknown

4) Clinical Management

a) All benzodiazepines can be expected to cross the placenta. [Teratogenicity](#) with [alprazolam](#) has not been confirmed; however, other benzodiazepines have demonstrated teratogenic potential [286]. Thus, use of [alprazolam](#) during pregnancy is not recommended. If pregnancy occurs during chronic use, the patient should be advised of the desirability of discontinuing the drug and of possible consequences to the fetus. If given, prescribe as monotherapy in the lowest effective dosage, for the shortest duration possible, and in divided doses to avoid high peak concentrations [287]. In contrast to benzodiazepines, the non-benzodiazepines [zolpidem](#) and [zaleplon](#) are in Pregnancy Risk Categories B and C, respectively [288] [289].

5) Literature Reports

a)) In a postmarketing evaluation of 276 liveborn infants exposed to [alprazolam](#) during the first trimester of pregnancy, the occurrence of congenital abnormalities in 13 infants (4.7%) was not considered unusual [282]. 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 [283]. When only cohort studies were pooled, no significant association between benzodiazepine use and major malformations was noted (odds ratio 0.90; 95% confidence interval 0.61 to 1.35; $p=0.62$); data pooled from case-control studies, however, showed a positive association with major malformations (odds ratio 3.01; 95% confidence interval 1.32 to 6.84; $p=0.008$). Similar observations were made with regard to oral cleft; the pooled cohort study data did not substantiate an association with drug use (odds ratio 1.19; 95% confidence interval 0.34 to 4.15; $p=0.997$), whereas the case-controlled data did (odds ratio 1.79; 95% confidence interval 1.13 to 2.82; $p=0.01$). Finally, the meta-analysis found two case-control studies that each provided conflicting evidence of any association between benzodiazepine exposure and cardiac malformations, and one study failed to find an association between exposure and central nervous system defects.

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 [284].

c)) Neonatal withdrawal symptoms following maternal ingestion have been associated with [diazepam](#), another benzodiazepine, and may occur with [alprazolam](#) [15] [285]. Symptoms included tremors, irritability, hyperactivity, hypertonicity, tachypnea, vigorous sucking, and in one case, weight loss, loose stools and vomiting; withdrawal symptoms may not be evident until several days after birth.

B)) Breastfeeding

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

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

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

3) Clinical Management

a) Human data is lacking regarding the use of [alprazolam](#) during breastfeeding; caution is advised. While the American Academy of Pediatrics identifies a number of benzodiazepines as having unknown effects of possible concern to a nursing infant [290], the World Health Organization considers the benzodiazepine [diazepam](#) safe during lactation when used occasionally in small doses [293].

4) Literature Reports

a) [Alprazolam](#) has been reported to result in symptoms of neonatal withdrawal in cases of maternal use of [alprazolam](#) during breastfeeding in addition to antepartum use [291]. Manufacturer product labeling states that infants who nurse from mothers on [diazepam](#), another benzodiazepine, may become lethargic and lose weight; labeling advises against nursing while on benzodiazepines [56] [292].

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.4 [305]

b) Active Metabolites

1) 4-hydroxy-alprazolam [305]

2) alpha-hydroxy-alprazolam [305]

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 [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

3.5.1.B) [Amiodarone](#)

1) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)

2) Summary: In vitro studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [amiodarone](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [amiodarone](#). Monitor for increased [alprazolam](#) side effects [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [alprazolam](#) and [amiodarone](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [amiodarone](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.

7) Probable Mechanism: inhibition by [amiodarone](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

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 [144] [145] [146] [147] [148].

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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.D) [Amprenavir](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (excessive sedation, confusion)
- 2) Summary: Serum concentrations of [alprazolam](#) may be elevated by the concurrent administration of [amprenavir](#). Currently no interaction study has been conducted. [Amprenavir](#) and [alprazolam](#) are both metabolized by cytochrome P450 3A4 enzymes, in addition to [amprenavir](#) inhibiting CYP3A4. Competition for metabolism and/or inhibition of metabolism could result in an increased plasma concentration of [alprazolam](#) [223].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Caution should be exercised if [alprazolam](#) and [amprenavir](#) are administered concurrently. The patient should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [alprazolam](#) metabolism by [amprenavir](#)

3.5.1.E] Anileridine

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].
- 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 [201].

3.5.1.F] Aprepitant

- 1) Interaction Effect: increased systemic exposure of benzodiazepines
- 2) Summary: [Aprepitant](#), a moderate CYP3A4 inhibitor, and fosaprepitant, a weak inhibitor of CYP3A4, can increase plasma concentrations of coadministered benzodiazepines that are CYP3A4 substrates (eg, [alprazolam](#), [midazolam](#), [triazolam](#)). Coadministration of [midazolam](#) (oral or IV) with oral [aprepitant](#) at doses of 125 mg or 80 mg, or fosaprepitant IV at doses of 100 mg or 150 mg, has resulted in increased [midazolam](#) AUC. Many of these increases were generally not considered to be clinically important. However, consideration should be given to the potential effects of increased plasma concentrations of benzodiazepines (ie, [midazolam](#), [triazolam](#), [alprazolam](#)) when they are coadministered with fosaprepitant or [aprepitant](#) [262] [263].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable

6j) Clinical Management: Coadministration of fosaprepitant or [aprepitant](#) with benzodiazepines metabolized by CYP3A4 (eg, [alprazolam](#), [midazolam](#), and [triazolam](#)) may result in increased benzodiazepine exposure. In studies conducted with [midazolam](#), coadministration of fosaprepitant or [aprepitant](#) under varying conditions resulted in increased [midazolam](#) AUC. Although many of the increases in [midazolam](#) AUC were generally not considered to be clinically important, depending on the particular situation, consideration of the potential effects of increased exposure to the benzodiazepine is recommended [262] [263].

7j) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of benzodiazepines

8j) Literature Reports

a) In an open-label, randomized, crossover study (n=10), coadministration of fosaprepitant 150 mg IV on day 1 with [midazolam](#) 2 mg orally on days 1 and 4 increased the [midazolam](#) AUC by 1.77-fold on day 1 compared with administration of [midazolam](#) alone [264]. [Midazolam](#) AUC was unchanged on day 4 [262] [263].

b) Coadministration of single doses of fosaprepitant 100 mg IV and oral [midazolam](#) 2 mg increased [midazolam](#) AUC by 1.6-fold [262] [263].

c) A single oral dose of [midazolam](#) 2 mg on day 1 and day 5 coadministered with oral [aprepitant](#) 125 mg on day 1 and 80 mg/day on days 2 through 5 increased [midazolam](#) AUC by 2.3-fold on day 1 and 3.3-fold on day 5 [262] [263].

d) Concomitant administration of [midazolam](#) 2 mg IV, given 1 hour after a single oral dose of [aprepitant](#) 125 mg, increased the [midazolam](#) AUC by 1.5-fold. Administration of [midazolam](#) 2 mg IV and oral [aprepitant](#) 125 mg on day 1, oral [aprepitant](#) 80 mg/day on days 2 and 3, and additional doses of [midazolam](#) 2 mg IV on days 4, 8, and 15 increased the [midazolam](#) AUC by 25% on day 4 and decreased the [midazolam](#) AUC by 19% on day 8. The [midazolam](#) AUC on day 15 was similar to baseline [262] [263].

3.5.1.G] Aprobarbital

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

2j) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].

3j) Severity: major

4j) Onset: unspecified

5j) Substantiation: probable

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

7j) Probable Mechanism: CNS depression

8j) Literature Reports

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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141].

A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.H] Boceprevir

- 1) Interaction Effect: increased [alprazolam](#) plasma concentrations
- 2) Summary: Coadministration of boceprevir, a strong CYP3A4 inhibitor [191], and [alprazolam](#), a CYP3A4 substrate [64], may lead to significantly increased [alprazolam](#) plasma concentrations. Although not studied with [alprazolam](#), concomitant use of boceprevir and oral [midazolam](#) (also a CYP3A4 substrate) resulted in significant increases in [midazolam](#) exposure and plasma concentration in a [pharmacokinetic study](#). If coadministration of [alprazolam](#) and boceprevir is necessary, consider a lower dose of [alprazolam](#). Closely monitor patient for [respiratory depression](#) and prolonged sedation [191].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [alprazolam](#) and boceprevir may lead to increased [alprazolam](#) plasma concentrations. If coadministration of [alprazolam](#) and boceprevir is necessary, consider a lower dose of [alprazolam](#). Closely monitor patient for [respiratory depression](#) and prolonged sedation [191].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by boceprevir
- 8) Literature Reports

a) In a [pharmacokinetic study](#) in healthy subjects or [hepatitis C](#) virus-positive (genotype-1) patients, concomitant administration of boceprevir 800 mg 3 times daily for 6 days and a single 4 mg oral dose of [midazolam](#) resulted in substantial increases in boceprevir AUC and C_{max}. The ratio of boceprevir mean C_{max} and AUC (with [midazolam](#) to without [midazolam](#)) was 2.77 (90% confidence interval (CI), 2.36 to 3.25) and 5.3 (90% CI, 4.66 to 6.03), respectively [191].

3.5.1.I] Brinzolamide

- 1) Interaction Effect: increased brinzolamide exposure
- 2) Summary: Concomitant use of brinzolamide (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of brinzolamide. If concomitant administration is required, use caution; however, accumulation of brinzolamide is unlikely because the main route of elimination is renal [163].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of brinzolamide (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of brinzolamide. If concomitant administration is required, use caution; however, accumulation of brinzolamide is unlikely because the main route of elimination is renal [163].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of brinzolamide

3.5.1.J] Butabarbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.K] Butalbital

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.L] Carbamazepine

- 1) Interaction Effect: decreased [alprazolam](#) plasma levels
- 2) Summary: Concomitant use of [alprazolam](#) and [carbamazepine](#) may result in a decrease in [alprazolam](#) plasma concentrations due to induction of CYP3A4-mediated metabolism of [alprazolam](#) by [carbamazepine](#) [149] [150] [62]. The addition of [carbamazepine](#) 600 mg daily to a patient stabilized on

alprazolam resulted in a significant decrease in alprazolam concentration (43 nanograms/milliliter [ng/mL] vs 20 ng/mL) [152]. If coadministered, monitor alprazolam effectiveness and consider dose adjustments if needed [149] [150].

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of alprazolam, a CYP3A4 substrate, and carbamazepine, a CYP3A4 inducer, may result in a decrease in alprazolam plasma concentrations [62]. If coadministering alprazolam and carbamazepine, monitor alprazolam effectiveness and consider dosage adjustments if needed [149] [150].

7) Probable Mechanism: induction of CYP3A4-mediated alprazolam metabolism by carbamazepine

8) Literature Reports

a) Combined therapy with alprazolam and carbamazepine was reported to result in significant reductions in alprazolam plasma levels, corresponding with clinical deterioration, in a 32-year-old man with atypical bipolar disorder and panic attacks. The patient was receiving oral lithium carbonate 1200 mg daily with oral alprazolam 7.5 mg daily prior to the initiation of carbamazepine. Carbamazepine 300 to 600 mg daily orally was used to control persistent impulsivity and psychosis; the lithium was discontinued [151].

3.5.1.M] 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 [159] [160]. 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 [159] [160]. 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.N] Carisoprodol

1) Interaction Effect: additive respiratory depression

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].

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] Chloral Hydrate

1) Interaction Effect: additive respiratory depression

- 2) Summary: [Chloral](#) hydrate, with a limited therapeutic index, can produce acute intoxication and [respiratory depression](#) [178]. 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.P] [Chlorzoxazone](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].
- 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.Q] [Cimetidine](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) 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) [123] [124] [125] [126]. Adverse effects such as pronounced sedation and impaired cognitive and psychomotor function have been reported [127] [128]. Benzodiazepines for which nitroreduction is a prominent metabolic pathway might also have their clearance decreased by [cimetidine](#) (eg, nitrazepam, [clonazepam](#)) [129] [130]. Those benzodiazepines eliminated primarily by glucuronidation do not interact with [cimetidine](#) (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)) [131] [132] [133] [134].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor for signs of benzodiazepine intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance). If symptoms are present, reduce benzodiazepine dose or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) The influence of [cimetidine](#) on [alprazolam](#) pharmacokinetics was evaluated in healthy subjects who ingested 1 mg [alprazolam](#) with and without concurrent [cimetidine](#) 300 mg every six hours [121]. The clearance of [alprazolam](#) was reduced from 1.66 mL/min/kg to 1.05 mL/min/kg (p less than 0.005).

b) The effect of concurrent [cimetidine](#) and [alprazolam](#) usage on [alprazolam](#) pharmacokinetics was evaluated. The clearance of [alprazolam](#) was markedly reduced with concurrent [cimetidine](#) administration [122].

3.5.1.R] Clarithromycin

- 1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [186] [187] [188] [189].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 ng/mL [183].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg TID for 3 days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [184].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following 5 days of [erythromycin](#) therapy versus placebo [185].

3.5.1.S] Cobicistat

- 1) Interaction Effect: increased concentrations of [alprazolam](#)
- 2) Summary: Using [alprazolam](#), a CYP3A4 substrate, together with a strong CYP3A4 inhibitor, such as cobicistat [272], should be avoided as this may result in elevated [alprazolam](#) plasma concentrations. Although not studied with cobicistat, concomitant use of [alprazolam](#) and [ketoconazole](#), also a potent CYP3A4 inhibitor, increased [alprazolam](#) plasma concentrations by 3.98-fold. If coadministration of [alprazolam](#) and a drug that inhibits CYP3A to a significant degree is required, dose reductions of [alprazolam](#) may be warranted [62] [61].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Using [alprazolam](#), a CYP3A4 substrate, together with a strong CYP3A4 inhibitor, such as cobicistat [272], should be avoided as this may result in elevated plasma [alprazolam](#) concentrations. If coadministration is required, dose reduction of [alprazolam](#) may be warranted [62] [61].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [alprazolam](#) by cobicistat
- 8) Literature Reports

a) Although not studied specifically with cobicistat, when [alprazolam](#) was coadministered with [ketoconazole](#), a potent CYP3A4 inhibitor, plasma [alprazolam](#) concentrations were increased in vivo by 3.98-fold. Coadministration of [alprazolam](#) and [ketoconazole](#) is contraindicated [62] [61].

3.5.1.T] Codeine

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

3.5.1.U] Crizotinib

1) Interaction Effect: increased exposure of drugs extensively metabolized by CYP3A4

2) Summary: Crizotinib is a moderate CYP3A4 inhibitor and concurrent use with drugs extensively metabolized by CYP3A4 may result in increased exposure of such drugs. Use caution when coadministering crizotinib and extensive CYP3A4 substrates. If concurrent use is clinically indicated, a dose reduction of the CYP3A4 substrate may be required [158].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution with coadministration of crizotinib and drugs extensively metabolized by CYP3A4, as crizotinib may increase the plasma concentrations of such drugs. If concurrent use is clinically indicated, dose reduction of drugs predominantly metabolized by CYP3A4 may be required [158].

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

8) Literature Reports

a) In a [pharmacokinetic study](#), coadministration of crizotinib (250 mg twice daily for 28 days) with oral [midazolam](#) resulted in a 3.7-fold increase in mean [midazolam](#) AUC compared with [midazolam](#) administered alone. This clinical study with a CYP3A4 substrate suggests that crizotinib is a moderate inhibitor of CYP3A4 [158].

3.5.1.V] Cyclosporine

1) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)

2) Summary: In vitro studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [cyclosporine](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [cyclosporine](#). Monitor for increased [alprazolam](#) side effects [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [alprazolam](#) and [cyclosporine](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [cyclosporine](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.

7) Probable Mechanism: inhibition by [cyclosporine](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.W] Dabrafenib

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: Concurrent administration of dabrafenib (a CYP3A4 inducer) with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. During drug interaction studies, dabrafenib decreased the AUC of [midazolam](#) (a CYP3A4 substrate) by 74%. Because a similar reaction can be expected with other CYP3A4 substrates, use of a drug other than a CYP3A4 substrate is recommended. If concomitant use cannot be avoided, monitor patients for loss of efficacy [193].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of dabrafenib, a CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If possible, substitute the use of CYP3A4 substrates during dabrafenib therapy. If concomitant use of dabrafenib and a CYP3A4 substrate is required, monitor patients for loss of efficacy [193].

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

8) Literature Reports

a) Administration of dabrafenib 150 mg twice daily for 15 days with a single 3 mg [midazolam](#) dose, decreased [midazolam](#) AUC by 74%. Dabrafenib is a CYP3A4 inducer, while [midazolam](#) is a CYP3A4 substrate [193].

3.5.1.X] Dantrolene

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].

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.Y] Deferasirox

1) Interaction Effect: reduced plasma concentrations of CYP3A4 substrate

2) Summary: Concomitant use of [deferasirox](#), a CYP3A4 inducer, and drugs that are metabolized by CYP3A4 may lead to decreased CYP3A4 substrate concentrations. Concomitant use [midazolam](#), a CYP3A4 substrate, and [deferasirox](#) resulted in decreases in the [midazolam](#) Cmax and AUC by 23% and 17%, respectively, in healthy volunteers. In the clinical setting, this effect may be more pronounced. Therefore, caution should be used when [deferasirox](#) is coadministered with other CYP3A4 substrates. If concomitant use is required, monitor patients for reduced effectiveness [212].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [deferasirox](#) and a CYP3A4 substrate such as escitalopram, [imatinib](#), and [tacrolimus](#), may result in decreased CYP3A4 substrate plasma concentrations. Therefore, caution is advised when [deferasirox](#) and drugs metabolized by CYP3A4 are coadministered and monitoring of patients for reduced effectiveness is recommended [212].

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

3.5.1.Z] Delavirdine

1) Interaction Effect: increased [alprazolam](#) concentrations

2) Summary: [Alprazolam](#) and delavirdine are both metabolized by the CYP3A4 enzyme system. Competition for this pathway could result in inhibition of [alprazolam](#) metabolism, creating the potential for [alprazolam](#) toxicity (excessive sedation, confusion). Concurrent administration of [alprazolam](#) and delavirdine is contraindicated [207].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [alprazolam](#) and delavirdine is contraindicated due to the potential for serious and/or life-threatening increase in sedation or [respiratory depression](#).

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

3.5.1.AA] Desipramine

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

2) Summary: [Desipramine](#) steady state plasma concentrations increased an average of 20% when used concomitantly with [alprazolam](#) at doses up to 4 mg/day. The clinical significance of this increase is unknown. A decrease in the [desipramine](#) dose should be considered for patients who are being treated with [alprazolam](#) and [desipramine](#) concurrently and who experience an increase in side effects such as dry eyes and mouth, constipation, decreased urination, or [arrhythmias](#) [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [alprazolam](#) and [desipramine](#) may increase the plasma concentrations of [desipramine](#). The clinical significance of this increase is unknown. If signs or symptoms of increased [desipramine](#) exposure such as blurred vision, dry mouth, constipation, urinary retention, or [arrhythmias](#) are noticed, a downward dosage adjustments of [desipramine](#) should be considered.

7) Probable Mechanism: unknown

3.5.1.AB] Desogestrel

1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive

8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AC] Dienogest

1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive

8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AD] Digoxin

1) Interaction Effect: [digoxin toxicity](#) (nausea, vomiting, [arrhythmias](#))

2) Summary: Concomitant administration of [alprazolam](#) or [diazepam](#) and [digoxin](#) has been reported to increase [digoxin](#) concentrations (5% to greater than 100%) [170]. Increased monitoring of [digoxin](#) levels are suggested when either adding or deleting [alprazolam](#) or [diazepam](#) therapy in patients stabilized on [digoxin](#) therapy [171] [172] [173].

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for signs of [digoxin](#) intoxication (eg, nausea, vomiting, diarrhea, persistent headache, confusion, fainting, visual disturbances). If symptoms are present, obtain a [digoxin](#) level and reduce dose accordingly.

7) Probable Mechanism: reduced renal clearance of [digoxin](#)

8) Literature Reports

a) Concomitant administration of [alprazolam](#) 1.5 mg per day and [digoxin](#) resulted in no change in [digoxin](#) clearance or other pharmacokinetic variables for [digoxin](#). In addition, [creatinine clearance](#) was not significantly affected during concomitant administration [168]. Therapeutic [alprazolam](#) doses should have no effect on [digoxin](#) serum concentrations. However, more studies are needed to evaluate the effect of higher [alprazolam](#) doses in seriously ill patients.

b) A 72-year-old nursing home female patient with atherosclerotic coronary [vascular disease](#) complicated by an anterior infarction and reversible [congestive heart failure](#) had a drug regimen which included oral [isosorbide](#), [furosemide](#), potassium [chloride](#), and oral [digoxin](#) (0.25 mg every morning except Sunday). Serum [digoxin](#) concentrations ranged from 1.6 to 1.8 ng/mL. The patient complained of insomnia, restlessness, and anxiety, and was started on [alprazolam](#) 1 mg at bedtime. During the second week of therapy, the patient had a number of non-specific complaints and was referred to the hospital. On admission, the serum [digoxin](#) concentration was 4.3 ng/mL. The patient's serum [creatinine](#) on admission was unchanged from previous visits. Both [digoxin](#) and [alprazolam](#) were discontinued. On her third hospital day, she developed [ventricular tachycardia](#) which required [lidocaine](#) administration. Oral [digoxin](#) was restarted at 0.125 mg per day. Follow-up steady-state [digoxin](#) concentration was 1.5 ng/mL [169].

3.5.1.AE] [Diltiazem](#)

1) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)

2) Summary: Clinical studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [diltiazem](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [diltiazem](#). Monitor for increased [alprazolam](#) side effects [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing [alprazolam](#) to patients who take [diltiazem](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.

7) Probable Mechanism: inhibition by [diltiazem](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.AF] [Domperidone](#)

1) Interaction Effect: increased domperidone exposure and an increased risk of QT prolongation

2) Summary: Coadministration of [alprazolam](#), a potential CYP3A4 inhibitor, with domperidone may result in increased plasma concentrations of domperidone and may have an effect on QT interval prolongation. Concomitant use of [alprazolam](#) and domperidone may increase the risk of serious cardiac events, including [ventricular arrhythmias](#) and sudden cardiac death, and therefore should be undertaken with caution. Case-control studies demonstrated an association of serious [ventricular arrhythmias](#) and sudden cardiac death, particularly with domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [200].

3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with the concomitant administration of [alprazolam](#) and domperidone as this may result in increased plasma concentrations of domperidone and may increase the risk of serious cardiac effects, including [ventricular arrhythmias](#) and sudden cardiac death, particularly at domperidone doses greater than 30 mg/day and in patients older than 60 years. Domperidone should be initiated at the lowest possible dose and titrated with caution. Discontinue domperidone if the patient experiences dizziness, palpitations, syncope, or seizure [200].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated domperidone metabolism

3.5.1.AG] [Drospirenone](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AH] [Elvitegravir](#)

- 1) Interaction Effect: increased concentrations of elvitegravir
- 2) Summary: Elvitegravir is metabolized by CYP3A4. Use caution when using elvitegravir in combination with a CYP3A4 inhibitor as this may cause increased elvitegravir plasma concentrations [269].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised when using elvitegravir, a CYP3A4 substrate, in combination with a CYP3A4 inhibitor as this may cause increased elvitegravir concentrations [269].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of elvitegravir

3.5.1.AI] [Ergotamine](#)

- 1) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)
- 2) Summary: In vitro studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [ergotamine](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [ergotamine](#). Monitor for increased [alprazolam](#) side effects [15].
- 3) Severity: moderate

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [alprazolam](#) and [ergotamine](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [ergotamine](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.
- 7) Probable Mechanism: inhibition by [ergotamine](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.AJ] [Erythromycin](#)

- 1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [239] [240] [241] [242].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance of [alprazolam](#)
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 ng/mL [236].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg TID for 3 days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [237].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following 5 days of [erythromycin](#) therapy versus placebo [238].

3.5.1.AK] [Eslicarbazepine Acetate](#)

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [119], use caution and monitor the patient closely.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [119], use caution and monitor the patient closely.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism by eslicarbazepine acetate

3.5.1.AL] Estradiol Cypionate

1) Interaction Effect: an increased risk of alprazolam toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may inhibit the oxidative metabolism of alprazolam, causing an increase in serum levels of the benzodiazepine. This may lead to psychomotor impairment after a single oral dose of alprazolam [167]. Therefore, monitoring for an increased response to alprazolam should be considered when concomitant use of alprazolam and a combination contraceptive is necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and alprazolam therapy for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of CYP3A4-mediated alprazolam metabolism by the contraceptive

8) Literature Reports

a) Concomitant oral contraceptive and alprazolam therapy has been reported to result in altered metabolism of alprazolam. In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of alprazolam following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of alprazolam may be enhanced in women taking oral contraceptives.

3.5.1.AM] Estradiol Valerate

1) Interaction Effect: an increased risk of alprazolam toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may inhibit the oxidative metabolism of alprazolam, causing an increase in serum levels of the benzodiazepine. This may lead to psychomotor impairment after a single oral dose of alprazolam [167]. Therefore, monitoring for an increased response to alprazolam should be considered when concomitant use of alprazolam and a combination contraceptive is necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and alprazolam therapy for an increased response to the benzodiazepine.

7) Probable Mechanism: inhibition of CYP3A4-mediated alprazolam metabolism by the contraceptive

8) Literature Reports

a) Concomitant oral contraceptive and alprazolam therapy has been reported to result in altered metabolism of alprazolam. In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of alprazolam following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of alprazolam may be enhanced in women taking oral contraceptives.

3.5.1.AN] Ethchlorvynol

1) Interaction Effect: additive respiratory depression

- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [179].
- 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] [Ethinyl Estradiol](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AP] [Ethinodiol Diacetate](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AQ| Etonogestrel

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.AR| 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 [174]. 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](#) [175]. 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 [174].
- 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 [174].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AS| Fluconazole

- 1) Interaction Effect: increased [alprazolam](#) concentrations and potential [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects)
- 2) Summary: Concomitant administration of [alprazolam](#) and [fluconazole](#) is not recommended [118]. If [alprazolam](#) is coadministered with [fluconazole](#), consider decreasing [alprazolam](#) dose and monitor for [alprazolam](#) toxicity (excessive sedation, fatigue, ataxia, slurred speech, slowed reactions, and other [psychomotor impairment](#)) [157].
- 3) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [alprazolam](#) and [fluconazole](#) is not recommended. Concurrent use of [alprazolam](#) and [fluconazole](#) may increase [alprazolam](#) concentrations and psychomotor effects. If concurrent use is required, consider reducing the dose of [alprazolam](#) and monitor for increased [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects).
- 7) Probable Mechanism: inhibition of the P450 3A4 enzyme system-mediated [alprazolam](#) metabolism by [fluconazole](#)
- 8) Literature Reports

a) Fluconazole is an inhibitor of cytochrome P450 3A (CYP3A) enzymes [157] [118] [114] [115]. Because the initial step in [alprazolam](#) metabolism is hydroxylation catalyzed by CYP3A, [fluconazole](#) may have a profound effect on the clearance of [alprazolam](#) [118].

3.5.1.AT] Fluoxetine

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (somnolence, dizziness, ataxia, slurred speech, hypotension, [psychomotor impairment](#))
- 2) Summary: Coadministered [fluoxetine](#) increases [alprazolam](#) serum concentrations [257] [258]. The mechanism of this interaction is thought to be inhibition by [fluoxetine](#) of the cytochrome P450 3A4 isoenzyme (CYP3A4), which is principally responsible for [alprazolam](#) metabolism. Some benzodiazepines ([lorazepam](#), [oxazepam](#)) are metabolized by glucuronidation rather than by the P450 system and may be the better choice for [fluoxetine](#) and benzodiazepine cotherapy.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients for signs and symptoms of [alprazolam](#) intoxication (somnolence, dizziness, ataxia, slurred speech, hypotension, [psychomotor impairment](#)). [Alprazolam](#) doses may need to be reduced. Alternatively, consider substituting a benzodiazepine (such as [lorazepam](#) or [oxazepam](#)) that has less potential for interacting with [fluoxetine](#).
- 7) Probable Mechanism: inhibition of cytochrome P450 3A-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) [Alprazolam](#) serum concentrations were analyzed in a double-blind, placebo-controlled study involving 80 healthy male volunteers [254]. Concurrent administration of [alprazolam](#) 1 mg four times a day and [fluoxetine](#) 60 mg each morning for four days resulted in a 30% increase in plasma [alprazolam](#) levels and a 21% decrease in the [alprazolam](#) elimination rate. The elevated [alprazolam](#) concentrations caused increased [psychomotor impairment](#), but did not affect mood status or sedation.

b) The effect of [fluoxetine](#) on the pharmacokinetics of [alprazolam](#) was analyzed in a 31-day, double-blind, crossover, placebo-controlled study, which included a 10-day washout period [255]. Twelve healthy male volunteers were given [fluoxetine](#) 20 mg twice a day or placebo and a single dose of [alprazolam](#) 1 mg on days 3 and 24. [Fluoxetine](#) significantly increased the half-life of [alprazolam](#) from 17 hours to 20 hours and significantly decreased its clearance from 61 mL/min to 48 mL/min.

c) Inhibition of [alprazolam](#) metabolism by [fluoxetine](#) occurs via cytochrome P450 3A4. A randomized, double-blind, placebo-controlled within subject design was used to assess this potential interaction. Twenty healthy volunteers attended four study sessions: [alprazolam](#)/placebo was given in the absence of an SSRI in the first two study sessions; [alprazolam](#)/placebo while

at steady-state with either [citalopram](#) 20 mg/day or [fluoxetine](#) 20 mg/day was given in the last two study sessions. At each session they received [alprazolam](#) 1 mg orally or placebo. [Fluoxetine](#) significantly prolonged the half-life of [alprazolam](#) by 16% and increased the area under the concentration-time curve by 32%. [Citalopram](#) did not affect these parameters. The effects of [alprazolam](#) were not altered by either SSRI. These findings suggest that [citalopram](#) and [fluoxetine](#) differentially alter [alprazolam](#) concentrations [256].

3.5.1.AU] [Fluvoxamine](#)

- 1) Interaction Effect: elevated plasma [alprazolam](#) levels and an increased risk of side effects (CNS depression)
- 2) Summary: [Fluvoxamine](#) coadministration (100 mg daily) with [alprazolam](#) 1 mg four times daily resulted in a 2-fold increase in [alprazolam](#) steady-state plasma concentrations, area under the concentration-time curve (AUC), maximum concentration (C_{max}), and half-life. Elevated plasma levels of [alprazolam](#) were associated with impaired psychomotor performance and memory. This effect may be even more pronounced with higher [fluvoxamine](#) doses (300 mg daily) [194].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: If [alprazolam](#) is given to a patient already on [fluvoxamine](#), the initial [alprazolam](#) dose should be reduced by 50% due to the possibility of significant [alprazolam](#) accumulation. Monitor for signs of [alprazolam](#) intoxication (eg, sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) or consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).
- 7) Probable Mechanism: inhibition by [fluvoxamine](#) of cytochrome P4503A4-mediated [alprazolam](#) metabolism

3.5.1.AV] [Fosamprenavir](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (excessive sedation, confusion, [respiratory depression](#))
- 2) Summary: Serum concentrations of [alprazolam](#) may be elevated by the concurrent administration of [fosamprenavir](#). [Amprenavir](#), the active metabolite of [fosamprenavir](#), and [alprazolam](#) are both metabolized by CYP3A4 isoenzymes and [amprenavir](#) is also an inhibitor of CYP3A4. Competition for metabolism and/or inhibition of metabolism could result in an increased plasma concentration of [alprazolam](#). Although clinical significance is unknown, a decrease in [alprazolam](#) dosing may be warranted [182].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution should be exercised if [alprazolam](#) and [fosamprenavir](#) are administered concurrently. The patient should be monitored for excessive benzodiazepine adverse effects, such as confusion, excessive sedation, and [respiratory depression](#). A decrease in [alprazolam](#) dose may be necessary [182].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by [amprenavir](#), the active metabolite of [fosamprenavir](#)

3.5.1.AW] [Fosaprepitant](#)

- 1) Interaction Effect: increased systemic exposure of benzodiazepines
- 2) Summary: [Aprepitant](#), a moderate CYP3A4 inhibitor, and [fosaprepitant](#), a weak inhibitor of CYP3A4, can increase plasma concentrations of coadministered benzodiazepines that are CYP3A4 substrates (eg,

alprazolam, midazolam, triazolam). Coadministration of midazolam (oral or IV) with oral aprepitant at doses of 125 mg or 80 mg, or fosaprepitant IV at doses of 100 mg or 150 mg, has resulted in increased midazolam AUC. Many of these increases were generally not considered to be clinically important. However, consideration should be given to the potential effects of increased plasma concentrations of benzodiazepines (ie, midazolam, triazolam, alprazolam) when they are coadministered with fosaprepitant or aprepitant [262] [263].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Coadministration of fosaprepitant or aprepitant with benzodiazepines metabolized by CYP3A4 (eg, alprazolam, midazolam, and triazolam) may result in increased benzodiazepine exposure. In studies conducted with midazolam, coadministration of fosaprepitant or aprepitant under varying conditions resulted in increased midazolam AUC. Although many of the increases in midazolam AUC were generally not considered to be clinically important, depending on the particular situation, consideration of the potential effects of increased exposure to the benzodiazepine is recommended [262] [263].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of benzodiazepines

8) Literature Reports

a) In an open-label, randomized, crossover study (n=10), coadministration of fosaprepitant 150 mg IV on day 1 with midazolam 2 mg orally on days 1 and 4 increased the midazolam AUC by 1.77-fold on day 1 compared with administration of midazolam alone [264]. Midazolam AUC was unchanged on day 4 [262] [263].

b) Coadministration of single doses of fosaprepitant 100 mg IV and oral midazolam 2 mg increased midazolam AUC by 1.6-fold [262] [263].

c) A single oral dose of midazolam 2 mg on day 1 and day 5 coadministered with oral aprepitant 125 mg on day 1 and 80 mg/day on days 2 through 5 increased midazolam AUC by 2.3-fold on day 1 and 3.3-fold on day 5 [262] [263].

d) Concomitant administration of midazolam 2 mg IV, given 1 hour after a single oral dose of aprepitant 125 mg, increased the midazolam AUC by 1.5-fold. Administration of midazolam 2 mg IV and oral aprepitant 125 mg on day 1, oral aprepitant 80 mg/day on days 2 and 3, and additional doses of midazolam 2 mg IV on days 4, 8, and 15 increased the midazolam AUC by 25% on day 4 and decreased the midazolam AUC by 19% on day 8. The midazolam AUC on day 15 was similar to baseline [262] [263].

3.5.1.AX] Fospropofol

1) Interaction Effect: additive cardiorespiratory effects

2) Summary: Concomitant use of fospropofol and a benzodiazepine may result in additive cardiorespiratory effects due to the sedative action of both drugs [96]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: CNS depression

3.5.1.AY] Haloperidol

- 1) Interaction Effect: increased [haloperidol](#) concentrations
- 2) Summary: Concurrent administration of [alprazolam](#), a CYP3A4 substrate [63], and [haloperidol](#) may increase the plasma concentrations of [haloperidol](#) via interference of CYP3A4-mediated [haloperidol](#) metabolism. In [pharmacokinetic studies](#), coadministration of CYP3A4 or CYP2D6 substrates or inhibitors and [haloperidol](#) resulted in mild to moderate increases in [haloperidol](#) plasma concentrations [206]. If the 2 drugs are coadministered, monitoring and dose adjustments may be required.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [alprazolam](#) and [haloperidol](#) may increase the plasma concentrations of [haloperidol](#) [206]. If the 2 drugs are coadministered, monitoring and dose adjustments may be required.
- 7) Probable Mechanism: interference with CYP3A4-mediated [haloperidol](#) metabolism

3.5.1.AZ] 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 [181].
- 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 [181].
- 7) Probable Mechanism: additive CNS depression

3.5.1.BA] Hydromorphone

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].
- 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 [201].

3.5.1.BB] [Imipramine](#)

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

2) Summary: [Imipramine](#) steady state plasma concentrations increased an average of 31% when used concomitantly with [alprazolam](#) at doses up to 4 mg/day. The clinical significance of this increase is unknown. A decrease in the [imipramine](#) dose should be considered for patients who are being treated with [alprazolam](#) and [imipramine](#) concurrently and who experience an increase in side effects such as dry eyes and mouth, constipation, decreased urination, or [arrhythmias](#) [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of [alprazolam](#) and [imipramine](#) may increase the plasma concentrations of [imipramine](#). The clinical significance of this increase is unknown. If signs or symptoms of increased [imipramine](#) exposure such as blurred vision, dry mouth, constipation, urinary retention, or [arrhythmias](#) are noticed, a downward dosage adjustments of [imipramine](#) should be considered.

7) Probable Mechanism: unknown

3.5.1.BC] [Indinavir](#)

1) Interaction Effect: an increased risk of serious [alprazolam](#) adverse effects (prolonged sedation, [respiratory depression](#))

2) Summary: Concomitant administration of [alprazolam](#) and [indinavir](#) is contraindicated as it may potentially cause serious and/or life-threatening reactions such as prolonged or increased sedation or [respiratory depression](#) [192]. [Alprazolam](#) is primarily metabolized by the CYP3A4 isozymes [1]. Coadministration with [indinavir](#), a CYP3A4 substrate and inhibitor, may result in increased levels of [alprazolam](#), which may cause serious [alprazolam](#) toxicity.

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of [alprazolam](#) and [indinavir](#) is contraindicated as use of this combination could potentially lead to serious and/or life-threatening reactions such as prolonged or increased sedation or [respiratory depression](#) [192].

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

3.5.1.BD] [Isoniazid](#)

1) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)

2) Summary: Clinical studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [isoniazid](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [isoniazid](#). Monitor for increased [alprazolam](#) side effects [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Concomitant use of [alprazolam](#) and [isoniazid](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [isoniazid](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.
- 7) Probable Mechanism: inhibition by [isoniazid](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.BE] [Itraconazole](#)

- 1) Interaction Effect: increased [alprazolam](#) concentrations and potential [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects)
- 2) Summary: Concurrent administration of [alprazolam](#) and [itraconazole](#) is contraindicated. Coadministration of [alprazolam](#) and [itraconazole](#) results in increased AUC and half-life of [alprazolam](#), decreased [alprazolam](#) clearance, and increased psychomotor effects of [alprazolam](#) [118] [161]. If concurrent use is required, consider reducing the dose of [alprazolam](#) and monitor for increased [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects) [162].
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant administration of [alprazolam](#) and [itraconazole](#) is contraindicated.
- 7) Probable Mechanism: inhibition of the P450 3A4 enzyme system-mediated [alprazolam](#) metabolism by [itraconazole](#)
- 8) Literature Reports

a) Studies have shown [itraconazole](#) to be a potent inhibitor of cytochrome P450 3A (CYP3A) enzymes, which is the enzyme responsible for hydroxylation of [alprazolam](#). In vivo studies have shown [alprazolam](#) concentrations increased by 2.7-fold when coadministered with [itraconazole](#). Concomitant administration of these two agents is contraindicated [118].

b) [Itraconazole](#) significantly increased plasma concentrations of [alprazolam](#) via its inhibitory effects on [alprazolam](#) metabolism and depressed psychomotor function during a double-blind, randomized crossover study involving ten healthy volunteers. Each study participant received [itraconazole](#) 200 mg daily or matching placebo for six days while ingesting a single oral dose of [alprazolam](#) 0.8 mg on day 4. [Itraconazole](#) increased the [alprazolam](#) area under the concentration-time curve (AUC) from 252 ng/h/mL to 671 ng/h/mL and decreased the oral clearance from 0.89 mL/min/kg to 0.35 mL/min/kg. Half-life of [alprazolam](#) was also extended from 15.7 hours to 40.3 hours. No significant differences were noted in the [alprazolam](#) maximum concentration (C_{max}) or the time to C_{max} (t_{max}) when [itraconazole](#) was present. Measurements of psychomotor function were evaluated by the digit symbol substitution test (DSST), the visual analog scale (VAS), and the Udalvg for kliniske undersogelser (UKU) scales. [Itraconazole](#) decreased the AUC (0-48) of the DSST and increased the "spacy" item of the VAS and the "sleepiness" item of the UKU. The depressed psychomotor function during [itraconazole](#) administration is likely explained by the elevated plasma [alprazolam](#) concentrations [161].

c) Azole antifungals, including [ketoconazole](#) are thought to inhibit the metabolism of drugs cleared by the cytochrome P450 3A subfamily of enzymes and, possibly, the P450 2C subfamily [114] [115].

3.5.1.BF] [Ivacaftor](#)

- 1) Interaction Effect: increased [alprazolam](#) exposure

- 2) Summary: [Alprazolam](#) is CYP3A4 substrate [61]. Although not specifically studied with [alprazolam](#), the concomitant administration of ivacaftor, a CYP3A inhibitor, and [midazolam](#), also a CYP3A4 substrate, increased [alprazolam](#) AUC by 1.5-fold. As a similar reaction can be expected with [alprazolam](#), caution and monitoring for benzodiazepine-related side effects are advised if these agents are coadministered [228].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution if [alprazolam](#) and ivacaftor are coadministered as this may result in increased [alprazolam](#) exposure. Monitor for benzodiazepine-related side effects [228].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism

3.5.1.BG] Josamycin

- 1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [219] [220] [221] [222].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in one hour by intravenous [erythromycin](#) 400 mg. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 mg/mL [216].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg three times daily for three days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from four to six hours, and decreased the volume of distribution [217].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following five days of [erythromycin](#) therapy versus placebo [218].

3.5.1.BH] Kava

- 1) Interaction Effect: increased central nervous system depression
- 2) Summary: Concomitant use of kava and [alprazolam](#) 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](#) [260]. In vitro data suggests this is most likely attributed to an increase in [GABA](#) binding sites in selected areas of the brain [261].

- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: It is advisable to avoid concomitant administration of kava and [alprazolam](#). For patients who use the combination, monitor closely for sedation, drowsiness, slowed reflexes, and other indicators of central nervous system depression.
- 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 [259].

3.5.1.BII] [Ketoconazole](#)

- 1) Interaction Effect: increased [alprazolam](#) concentrations and potential [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects)
- 2) Summary: Coadministration of [alprazolam](#) with [ketoconazole](#) is contraindicated [117] [118]. [Alprazolam](#) exposure increased 4-folds when coadministered with [ketoconazole](#) in healthy volunteers [113]. Monitor patients for [alprazolam](#) toxicity (excessive sedation and prolonged hypnotic effects) when these 2 drugs are administered together.
- 3) Severity: contraindicated
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant administration of [alprazolam](#) and [ketoconazole](#) is contraindicated.
- 7) Probable Mechanism: inhibition of the P450 3A4 enzyme system-mediated [alprazolam](#) metabolism by [ketoconazole](#)
- 8) Literature Reports

a) Studies have shown [ketoconazole](#) to be a potent inhibitor of cytochrome P450 3A (CYP3A) enzymes, which is the enzyme responsible for hydroxylation of [alprazolam](#). In vivo studies have shown [alprazolam](#) concentrations were increased by 3.98-fold when coadministered with [ketoconazole](#). Concomitant administration of these two agents is contraindicated [112].

b) Seven healthy male volunteers participated in a double-blind, single-dose, 5-way crossover study to determine the magnitude and clinical consequence of the interaction of [ketoconazole](#) with [alprazolam](#). The five treatment phases consisted of placebo and [alprazolam](#) 1 mg, [ketoconazole](#) 200 mg and [alprazolam](#) 1 mg, and [ketoconazole](#) 200 mg and placebo. The elimination half-life of [alprazolam](#) increased from 15.2 hours to 59 hours during [ketoconazole](#) coadministration, while the total area under the concentration-time curve (AUC) of [alprazolam](#) rose from 237 ng/mL/h to 944 ng/mL/h. The oral clearance of [alprazolam](#) decreased from 86 mL/min to 27 mL/min. However, the peak plasma concentrations were not significantly altered by the presence of [ketoconazole](#). Pharmacodynamically, [ketoconazole](#) enhanced the benzodiazepine effects of [alprazolam](#) but statistical significance was not always achieved due to the degree of variability and the small sample size [113].

c) Azole antifungals, including [ketoconazole](#) are thought to inhibit the metabolism of drugs cleared by the cytochrome P450 3A subfamily of enzymes and, possibly, the P450 2C subfamily [114] [115].

d)) **Ketoconazole** was found to be a potent inhibitor of **alprazolam** metabolism in an in vitro study. The effects of **ketoconazole**, **quinidine**, and serotonin-reuptake-inhibitor antidepressants on the metabolism of **alprazolam** was studied. In this report, the cytochrome P450 3A subfamily of enzymes appeared to mediate **alprazolam** metabolism [116].

3.5.1.BJ] **Levonorgestrel**

- 1)) Interaction Effect: an increased risk of **alprazolam** toxicity (CNS depression, hypotension)
- 2)) Summary: Combination contraceptives may inhibit the oxidative metabolism of **alprazolam**, causing an increase in serum levels of the benzodiazepine. This may lead to **psychomotor impairment** after a single oral dose of **alprazolam** [167]. Therefore, monitoring for an increased response to **alprazolam** should be considered when concomitant use of **alprazolam** and a combination contraceptive is necessary.
- 3)) Severity: moderate
- 4)) Onset: delayed
- 5)) Substantiation: probable
- 6)) Clinical Management: Monitor patients receiving concurrent combination contraceptives and **alprazolam** therapy for an increased response to the benzodiazepine.
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated **alprazolam** metabolism by the contraceptive
- 8)) Literature Reports

a)) Concomitant oral contraceptive and **alprazolam** therapy has been reported to result in altered metabolism of **alprazolam**. In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of **alprazolam** following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of **alprazolam** may be enhanced in women taking oral contraceptives.

3.5.1.BK] **Levorphanol**

- 1)) Interaction Effect: additive **respiratory depression**
- 2)) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when **meperidine** and benzodiazepines are used concomitantly. Administration of reduced doses of **meperidine** is recommended [203]. 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** [175].
- 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 [201].

3.5.1.BL] **Lomitapide**

- 1)) Interaction Effect: increased exposure of lomitapide

2) Summary: The concomitant use of lomitapide (a CYP3A4 substrate) with a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. Cross-study comparisons with concurrent use of lomitapide and oral contraceptives, which are weak CYP3A4 inhibitors, illustrate an approximate 2-fold increase in lomitapide exposure. If concurrent use is required, limit lomitapide dosage to 30 mg daily [120]. Consider additional monitoring as necessary.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of lomitapide (a CYP3A4 substrate) with a weak CYP3A4 inhibitor may cause increased exposure to lomitapide. If concurrent use is required, limit lomitapide dosage to 30 mg daily [120]. Consider additional monitoring as necessary.

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of lomitapide

3.5.1.BM] 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 [176] and use with caution [177].

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 [176] and use with caution [177].

7) Probable Mechanism: additive CNS depression

3.5.1.BN] 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](#) [243] [244] [245] 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](#) [243] [244] [245] 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.BO] Medroxyprogesterone Acetate

1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)

2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single

oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

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

7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive

8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.BP] [Meperidine](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

3.5.1.BQ] [Mephesisin](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

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

7) Probable Mechanism: CNS depression

3.5.1.BR] [Mephobarbital](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.BS] [Meprobamate](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].
- 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.BT] [Mestranol](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a)) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.BU] [Metaxalone](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].
- 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.BV] [Methocarbamol](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [265] [266] [267] [268].
- 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.BW] [Methohexital](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.BX] [Mifepristone](#)

- 1) Interaction Effect: increased [alprazolam](#) exposure
- 2) Summary: [Alprazolam](#) is primarily metabolized by CYP3A4 [61] and [mifepristone](#) is a CYP3A4 inhibitor. In a [pharmacokinetic study](#), compared with [alprazolam](#) administration alone, the coadministration of [alprazolam](#) with [mifepristone](#) (Korlym(TM)) resulted in an [alprazolam](#) AUC mean ratio (with/without) of 1.8. When concurrent therapy is indicated, use of the lowest clinically effective [alprazolam](#) dose along with therapeutic monitoring and follow up. Due to the long terminal half-life of [mifepristone](#) after reaching steady state, allow at least 2 weeks following cessation of [mifepristone](#) (Korlym(TM)) before increasing the dose of [alprazolam](#) [213].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: probable
- 6) Clinical Management: Caution is advised with concomitant use of [alprazolam](#) and [mifepristone](#) due to the potential for increased [alprazolam](#) exposure. Use the lowest effective dose of [alprazolam](#) along with therapeutic monitoring and follow up. Due to the long terminal half-life of [mifepristone](#) after reaching steady state, allow at least 2 weeks following cessation of [mifepristone](#) (Korlym(TM)) increasing the dose of [alprazolam](#) [213].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) In a [pharmacokinetic study](#), the concomitant administration of a single oral dose of [alprazolam](#) 1 mg in healthy subjects receiving [mifepristone](#) 1200 mg once daily for 10 days resulted in increased [alprazolam](#) exposure. Compared with [alprazolam](#) administration alone, coadministration with [mifepristone](#) resulted in an AUC and Cmax geometric mean ratio of 1.8 and 0.81, respectively for [alprazolam](#), and 0.76 and 0.39, respectively for the 4-hydroxy-alprazolam metabolite [213].

3.5.1.BY] [Mitotane](#)

- 1) Interaction Effect: decreased exposure of CYP3A4 substrates
- 2) Summary: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [190] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concurrent administration of [mitotane](#), a strong CYP3A4 inducer, with a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If concomitant use is required, monitor patients to determine dosage adjustments [190] and loss of efficacy. If possible, substitute the use of CYP3A4 substrates during [mitotane](#) therapy.
- 7) Probable Mechanism: induction of CYP3A4-mediated metabolism by [mitotane](#)

3.5.1.BZ] [Morphine](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

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

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

3.5.1.CB] [Nefazodone](#)

1) Interaction Effect: [psychomotor impairment](#) and sedation

2) Summary: Concomitant administration of [alprazolam](#) 1 mg twice daily and [nefazodone](#) 200 mg twice daily resulted in an almost two-fold increase in [alprazolam](#) plasma concentration, area under the concentration-time curve (AUC), and half-life, leading to alprazolam-induced [psychomotor impairment](#) and sedation. Nefazodone is an inhibitor of cytochrome P450 3A4, the same enzyme system which metabolizes [alprazolam](#). [Nefazodone](#) plasma concentration was not affected by the coadministration of [alprazolam](#) [247] [248] [249].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

- 6j) Clinical Management: Caution is warranted if [alprazolam](#) and [nefazodone](#) are to be coadministered. Initially [alprazolam](#) doses should be reduced by 50%. Carefully monitor patients for signs of [psychomotor impairment](#) or excessive sedation. [Nefazodone](#) doses are not likely to require adjustment.
- 7j) Probable Mechanism: inhibition of cytochrome P450-mediated [alprazolam](#) metabolism
- 8j) Literature Reports

a) Forty-eight healthy male volunteers participated in a randomized, double-blind, parallel-group, placebo-controlled fashion to determine the effect of [nefazodone](#) administration on the pharmacokinetics of [alprazolam](#). Subjects received either placebo twice daily, [alprazolam](#) 1 mg twice daily, [nefazodone](#) 200 mg twice daily, or a combination of [alprazolam](#) 1 mg and [nefazodone](#) 200 mg twice daily for seven days. [Nefazodone](#) significantly increased the maximum concentration (C_{max}) of [alprazolam](#) approximately two-fold while the C_{max} of the alpha-hydroxy [alprazolam](#) metabolite decreased by 40%. [Alprazolam](#) is hydroxylated to form 4-hydroxy [alprazolam](#) and alpha-hydroxy [alprazolam](#) by cytochrome P450 3A4 enzymes, and [nefazodone](#) has been shown in vitro to be an inhibitor of this isoenzyme [246].

3.5.1.CC] [Nicardipine](#)

- 1j) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)
- 2j) Summary: In vitro studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [nicardipine](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [nicardipine](#). Monitor for increased [alprazolam](#) side effects [15].
- 3j) Severity: moderate
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: Concomitant use of [alprazolam](#) and [nicardipine](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [nicardipine](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.
- 7j) Probable Mechanism: inhibition by [nicardipine](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.CD] [Nifedipine](#)

- 1j) Interaction Effect: increased bioavailability and pharmacodynamic effects of [alprazolam](#)
- 2j) Summary: In vitro studies with benzodiazepines other than [alprazolam](#) suggest concomitant administration of [alprazolam](#) and [nifedipine](#) may result in an increase in the bioavailability of [alprazolam](#) due to inhibition of CYP3A-mediated [alprazolam](#) metabolism. Caution should be used with concurrent use of [alprazolam](#) and [nifedipine](#). Monitor for increased [alprazolam](#) side effects [15].
- 3j) Severity: moderate
- 4j) Onset: unspecified
- 5j) Substantiation: theoretical
- 6j) Clinical Management: Concomitant use of [alprazolam](#) and [nifedipine](#) may cause elevated [alprazolam](#) plasma concentrations. Use caution when prescribing [alprazolam](#) to patients who take [nifedipine](#). Monitor for increased [alprazolam](#) side effects including drowsiness or fatigue, nausea, vomiting, diarrhea or constipation.
- 7j) Probable Mechanism: inhibition by [nifedipine](#) of cytochrome P4503A-mediated [alprazolam](#) metabolism

3.5.1.CE| Norelgestromin

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.CF| Norethindrone

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.CG| Norgestimate

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate

- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.CH] [Norgestrel](#)

- 1) Interaction Effect: an increased risk of [alprazolam](#) toxicity (CNS depression, hypotension)
- 2) Summary: Combination contraceptives may inhibit the oxidative metabolism of [alprazolam](#), causing an increase in serum levels of the benzodiazepine. This may lead to [psychomotor impairment](#) after a single oral dose of [alprazolam](#) [167]. Therefore, monitoring for an increased response to [alprazolam](#) should be considered when concomitant use of [alprazolam](#) and a combination contraceptive is necessary.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and [alprazolam](#) therapy for an increased response to the benzodiazepine.
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by the contraceptive
- 8) Literature Reports

a) Concomitant oral contraceptive and [alprazolam](#) therapy has been reported to result in altered metabolism of [alprazolam](#). In one controlled study, low-dose estrogen oral contraceptives produced a significant increase in AUC and decreased the elimination rate of [alprazolam](#) following single-dose administration (1 mg) [166]. Patient response to therapeutic doses of [alprazolam](#) may be enhanced in women taking oral contraceptives.

3.5.1.CI] [Omeprazole](#)

- 1) Interaction Effect: benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Concurrent use of [diazepam](#) and [omeprazole](#) has been reported to slow [diazepam](#) metabolism and delay its elimination, thereby resulting in enhanced and prolonged benzodiazepine effects [250] [251] [252]. One study indicated that decreased [diazepam](#) clearance occurred in almost half of patients who were fast metabolizers of [omeprazole](#) but the combination had little significance in slow metabolizers of [omeprazole](#) [253]. Although not yet reported for combined [alprazolam](#)-[omeprazole](#) therapy, similar effects would be expected to occur. [Lorazepam](#), [oxazepam](#), and [temazepam](#) are benzodiazepines that are metabolized by glucuronidation rather than by the cytochrome P450 enzyme system and may be good alternatives for patients needing [omeprazole](#) and benzodiazepine therapy.
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: With concurrent administration, monitor patients for CNS depression (sedation, lethargy, speech difficulties), and adjust doses accordingly. Consider switching to a benzodiazepine eliminated by glucuronidation (eg, [lorazepam](#), [oxazepam](#), [temazepam](#)).

7J) Probable Mechanism: slowed benzodiazepine metabolism and clearance

3.5.1.CJ] Oxycodone

1J) Interaction Effect: increased CNS or [respiratory depression](#)

2J) 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 [224] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [225].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [224] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [225].

7J) Probable Mechanism: additive effects

3.5.1.CK] Oxymorphone

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

2J) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

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

7J) Probable Mechanism: CNS depression

8J) Literature Reports

aJ) Concomitant [propoxyphene](#) (65 mg every six hours) and [alprazolam](#) (1 mg) therapy has been reported to increase the half-life of [alprazolam](#) by greater than 50% (11 vs 18 h), which may lead to excessive CNS depression [201].

3.5.1.CL] Pentobarbital

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

2J) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: probable

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

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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.CM] 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 [180].

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 [180].

7) Probable Mechanism: additive CNS depression

3.5.1.CN] [Phenobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].

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 [135] [136] [137] [138] [139].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.CO| Piperazine

- 1)) Interaction Effect: increased exposure of piperazine and CYP3A4 substrates
- 2)) Summary: The concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and the risk for QT prolongation. If concomitant use is required, [ECG monitoring](#) should be considered. Additionally, concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors or a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [215].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of piperazine (a CYP3A4 substrate) with a CYP3A4 inhibitor may increase the exposure of piperazine and increase the risk for QT-interval prolongation. If concomitant use is required, [ECG monitoring](#) should be considered. Additionally, concurrent administration of piperazine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperazine, caution is advised when administering CYP3A4 inhibitors or a CYP3A4 substrate for up to 3 months after discontinuation of piperazine therapy [215].
- 7)) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of piperazine; inhibition of CYP3A4-mediated metabolism of this drug by piperazine

3.5.1.CP| [Primidone](#)

- 1)) Interaction Effect: additive [respiratory depression](#)
- 2)) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.CQ| [Propoxyphene](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].
- 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 [201].

3.5.1.CR| [Remifentanyl](#)

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].
- 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 [201].

3.5.1.CS| [Rifampine](#)

- 1) Interaction Effect: reduced [diazepam](#) plasma concentrations and effectiveness

2) Summary: Concurrent use of [rifapentine](#) and a benzodiazepine has resulted in reduced benzodiazepine serum concentrations and effectiveness. [Rifapentine](#) probably induces hepatic microsomal enzymes which metabolizes the benzodiazepine [271].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If used concurrently, a dosage adjustment for the benzodiazepine may be required in order to maintain a therapeutic effect. Dosage reduction may be required after discontinuing [rifapentine](#).

7) Probable Mechanism: induction of benzodiazepine metabolism

3.5.1.CT] [Ritonavir](#)

1) Interaction Effect: increased plasma concentrations of [alprazolam](#) and enhanced [alprazolam](#) effects

2) Summary: When [alprazolam](#) 1 mg was administered as a single dose to 12 patients who had been receiving [ritonavir](#) 500 mg twice daily for ten days, the area under the concentration-time curve (AUC) of [alprazolam](#) decreased by 12% and the maximum concentration (C_{max}) decreased by 16% [209]. Early exposure to low-dose [ritonavir](#) (200 mg twice daily) has resulted in an increase in the [alprazolam](#) half-life from 13.1 hours to 22.7 hours and has decreased the oral clearance from 88 mL/min to 32 mL/min. Administration of low doses of [ritonavir](#) for a short duration of time resulted in a reduction in [alprazolam](#) clearance enhancement of clinical effects [210]. Clinical significance is unknown; however, a decrease in benzodiazepine dose may be needed [211].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving [alprazolam](#) and [ritonavir](#) should be monitored for enhanced sedative effects.

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

8) Literature Reports

a) Ten healthy HIV-seronegative volunteers were involved in a double-blind, randomized, two-way crossover design study. The results of the study indicate that a highly significant prolongation of half-life and impairment of clearance of [alprazolam](#), a cytochrome P450 3A (CYP3A) substrate, occurs with short-term exposure to low doses of [ritonavir](#). [Alprazolam](#) clearance was reduced to 30% to 50% of control values. The results of this study suggest that there is an initial inhibitory effect of [ritonavir](#) on CYP3A-mediated drug metabolism. The long term effects of [ritonavir](#) on the pharmacokinetics of [alprazolam](#) are unknown, however. The authors conclude that drugs which demonstrate different metabolic and interaction traits under short-term and long-term therapy conditions need careful assessment before definitive guidelines can be established [208].

3.5.1.CU] [Roxithromycin](#)

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

2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [232] [233] [234] [235].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller

benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.

7) Probable Mechanism: decreased hepatic metabolism; decreased clearance

8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in one hour by intravenous [erythromycin](#) 400 mg. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated ([midazolam](#) 0.5 mg/kg and [atropine](#) 0.03 mg/kg) but did not receive [erythromycin](#) had a mean [midazolam](#) level of 73 mg/mL [229].

b) In a study involving normal volunteers, [erythromycin](#) (333 mg three times daily for three days) increased the peak levels of [triazolam](#) by 50%, increased the half-life from four to six hours, and decreased the volume of distribution [230].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered [midazolam](#) is reduced by about 50% following five days of [erythromycin](#) therapy versus placebo [231].

3.5.1.CV] [Saquinavir](#)

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

2) Summary: [Alprazolam](#) is metabolized primarily by CYP3A4 and [saquinavir](#) is a strong CYP3A4 inhibitor. Although not directly studied, the coadministration of [alprazolam](#) with [ketoconazole](#) and [itraconazole](#) (other strong CYP3A4 inhibitors) increased the [alprazolam](#) plasma concentrations by 3.98-fold and 2.7-fold, respectively. When possible, the concomitant use of [alprazolam](#) with [saquinavir](#) should be avoided; however, if coadministration is necessary, [alprazolam](#) dose reductions may be warranted [204] [59].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of [alprazolam](#) with [saquinavir](#) should generally be avoided. If coadministration is required, a dose reduction of [alprazolam](#) may be warranted [59].

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

3.5.1.CW] [Secobarbital](#)

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

2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].

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 [135] [136] [137] [138] [139].

b)) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.CX] [Sertraline](#)

1)) Interaction Effect: an increased risk of [psychomotor impairment](#) and sedation

2)) Summary: To date, limited information is available related to the effects of coadministered [alprazolam](#) and [sertraline](#). One study found that [sertraline](#) was a moderate inhibitor in vitro of [alprazolam](#) metabolism [154]. It is theoretically possible that an interaction might occur because [alprazolam](#) is metabolized by the cytochrome P450 3A system and [sertraline](#) is thought to inhibit one or more P450 isoenzymes [155]. Current evidence indicates that [alprazolam](#) is metabolized at least in part by the CYP3A family of isoenzymes and [sertraline](#) is suspected of inhibiting the CYP3A4 isoenzyme. However, a study involving ten healthy volunteers failed to show an alteration in the pharmacokinetics or pharmacodynamics of [alprazolam](#) when given with [sertraline](#) [156].

3)) Severity: moderate

4)) Onset: rapid

5)) Substantiation: probable

6)) Clinical Management: Caution is warranted if [alprazolam](#) and [sertraline](#) are to be coadministered. Monitor patients for signs of [psychomotor impairment](#) or excessive sedation. [Alprazolam](#) doses may need to be reduced.

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

8)) Literature Reports

a)) Ten healthy white volunteers (eight women and two men) participated in a randomized, double-blind, placebo-controlled study to determine whether therapeutic doses of [sertraline](#) have the potential to impair [alprazolam](#) metabolism and to assess whether any potential impairment is dependent on [sertraline](#) dose. Study participants received [alprazolam](#) 1 mg orally or placebo and [sertraline](#) 50 mg, 100 mg, or 150 mg daily. The [alprazolam](#) maximum concentration (C_{max}), time to maximum concentration (t_{max}), half-life, and area under the concentration-time curve (AUC) were not clinically significantly altered in the presence of [sertraline](#). No pharmacodynamic interactions, as measured by sedation, digit-symbol substitution test, immediate recall, and delayed recall, were detected between [sertraline](#) and [alprazolam](#) at any dose of [sertraline](#). These in vivo findings are contrary to in vitro data which suggest that [sertraline](#) inhibits [alprazolam](#) metabolism via cytochrome P450 3A4 enzymes [153].

3.5.1.CY] [Sodium Oxybate](#)

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

2)) Summary: In trials involving [sodium oxybate](#), [respiratory depression](#) was reported [97]. When used in combination with benzodiazepines, these drugs may have additive CNS and respiratory depressant effects.

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

3.5.1.CZ] 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 [195] [196] [197] [198]. St. John's wort did not, however, significantly affect [quazepam](#) efficacy [195]. 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 [195] [196] [197] [198]. 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 [195].

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) [196].

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 [199].

d) St. John's wort reduced the bioavailability of oral [midazolam](#) by 50% after 14 days in an open-label study of 12 healthy subjects, while single dose St. John's wort had no effect. In the short-term study, subjects took St. John's wort (Sundown Herbals, Boca Raton, FL) 300 mg one hour prior to a single dose of intravenous [midazolam](#) 0.05 mg/kg. Oral [midazolam](#) syrup 5 mg was administered 24 hours after St. John's wort. In the long-term study, subjects took St. John's wort 300 mg three times daily for 14 to 15 days followed by the same [midazolam](#) doses. St. John's wort was from a single lot and was labeled to contain 900 mcg hypericin. Ten randomly selected capsules tested contained 840 +/- 56 mcg hypericin and 11 +/- 0.63 mg hyperforin. Following 14 days of St. John's wort use, AUC and Cmax of oral [midazolam](#) were reduced by 50%, and oral clearance increased 2-fold (all p less than 0.05). AUC of intravenous [midazolam](#) was nonsignificantly reduced by 21%. These results suggest that St. John's wort increased first-pass elimination of [midazolam](#) with reduced availability likely due to CYP3A4 induction at the gut wall [197].

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) [198].

3.5.1.DA] [Sufentanil](#)

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

2) Summary: When used in combination, these drugs have additive CNS and respiratory depressant effects [202]. Hypotension, profound sedation or coma may result when [meperidine](#) and benzodiazepines are used concomitantly. Administration of reduced doses of [meperidine](#) is recommended [203]. 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](#) [175].

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 [201].

3.5.1.DB] 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 [227]. While this is likely responsible for anxiolytic activity of tan-shen, it appears that sedation, muscle relaxation, and addiction qualities are minimized [227]. 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) [226]. 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](#) [226].

3.5.1.DC] 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 [165].
- 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 [165].
- 7) Probable Mechanism: additive effects

3.5.1.DD] Teduglutide

- 1) Interaction Effect: increased exposure of orally administered benzodiazepines
- 2) Summary: Coadministration of teduglutide with an oral medication that requires titration, such as a benzodiazepine, may significantly increase absorption of the benzodiazepine. In clinical trials, a patient taking a benzodiazepine who was treated with concomitant teduglutide experienced altered mental status that progressed to coma. A reduced dose of oral drugs requiring titration (eg, benzodiazepines) may be necessary when administered concomitantly with teduglutide [205]. If coadministration is necessary, the patient should be monitored for increased benzodiazepine side effects.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised if teduglutide is coadministered with an oral medication that requires titration, such as a benzodiazepine. Concomitant use may cause increased absorption of benzodiazepines and require dose adjustment of the orally administered benzodiazepine [205]. Monitor for increased benzodiazepine side effects if a patient is taking teduglutide concomitantly with an oral benzodiazepine.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a placebo-controlled clinical trial of teduglutide in adults with [short bowel syndrome](#) who were dependent on parenteral nutrition support, 1 woman who received teduglutide 0.05 mg/kg/day with concomitant oral [prazepam](#) had a dramatic deterioration in mental status, progressing to coma during the first week of study treatment. The level of [prazepam](#) in her blood was more than 300 mcg/L upon being admitted to the ICU. The coma resolved 5 days after teduglutide and [prazepam](#) were discontinued [205].

3.5.1.DE] Telaprevir

- 1) Interaction Effect: increased [alprazolam](#) exposure
- 2) Summary: In a [pharmacokinetic study](#) (n=17), concomitant administration of [alprazolam](#), a CYP3A4 substrate [64], and telaprevir increased [alprazolam](#) exposure by 35%. If coadministration of these agents is necessary, clinical monitoring of patients is recommended [214].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of [alprazolam](#) and telaprevir may lead to increased [alprazolam](#) exposure. If coadministration of [alprazolam](#) and telaprevir is necessary, clinical monitoring of patients is recommended [214].
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism
- 8) Literature Reports

a) In a [pharmacokinetic study](#) in healthy subjects or [chronic hepatitis C](#) patients (n=17), concomitant administration of a single-dose of [alprazolam](#) 0.5 mg and telaprevir 750 mg every 8 hours for 10 days resulted in increased in [alprazolam](#) AUC (ratio estimate (with telaprevir to without telaprevir), 1.35 (90% confidence interval, 1.23 to 1.49) [214].

3.5.1.DF] Theophylline

- 1) Interaction Effect: decreased benzodiazepine effectiveness

2) Summary: [Theophylline](#) has been shown to reverse the sedative effects of benzodiazepines [107] [108] [109] [110]. A larger dose of benzodiazepine may be needed to produce sedation in a theophylline-treated patient. [Respiratory depression](#) may occur if [theophylline](#) is discontinued without a reduction of the benzodiazepine dose [111].

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor the patient for benzodiazepine clinical effectiveness. A larger than usual benzodiazepine dose may be required in a theophylline-treated patient. Benzodiazepine toxicity ([respiratory depression](#), sedation, dizziness, ataxia, weakness, decreased cognition or motor performance) may occur if [theophylline](#) is discontinued without a subsequent reduction in the benzodiazepine dose.

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

8) Literature Reports

a) Eight healthy male volunteers participated in a study which demonstrated the antagonistic properties of [theophylline](#) on diazepam-induced [psychomotor impairment](#). Subjects received an oral dose of [diazepam](#) 0.25 mg/kg, followed 40 minutes later by an intravenous infusion of 100 mL normal saline with or without [theophylline](#) 4.4 mg/kg. All subjects were tested twice: one time receiving [theophylline](#) and the other time receiving placebo. [Theophylline](#) reversed some of the diazepam-induced [psychomotor impairment](#) as measured by the digit symbol substitution test, card sorting, and three questionnaires which measured mood, anxiety, and distress. The antagonism caused by [theophylline](#) may be attributed to the stimulant action caused by methylxanthines on the central nervous system through [adenosine](#) receptor blockade [98].

b) Intravenous [theophylline](#) was reported to reverse the sedation produced by intravenous [diazepam](#) in patients undergoing [genitourinary surgery](#). Patients were given intravenous doses of [diazepam](#) during surgery to maintain deep sedation, followed by administration of intravenous [aminophylline](#) (60 to 120 mg) or normal saline postoperatively. Rapid [reversal of sedation](#) occurred in [aminophylline](#) patients as compared to no response in saline patients [99]. Other studies and case reports have also shown that [theophylline](#) antagonizes the sedative effects of [diazepam](#) [100] [101].

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

d) Less successful rates have been reported when utilizing [aminophylline](#) to reverse benzodiazepine oversedation. Of the six patients reported, all of whom had received [midazolam](#), five patients showed no change in the level of consciousness after the administration of [aminophylline](#) 75 mg. One patient did experience quick and sudden awakening after [aminophylline](#) was given. The author suggests that there may be wide individual variations within the population to the effects of [aminophylline](#) antagonism on benzodiazepines [105].

e) To determine the mechanism by which [theophylline](#) antagonizes benzodiazepines, oral [alprazolam](#) 1 mg daily for seven days was administered to six patients who were receiving [theophylline](#) and to seven patients who were not receiving [theophylline](#) treatment. Serum [alprazolam](#) levels were significantly lower in patients on concurrent [theophylline](#) therapy, and the levels continued to decrease during each day of the study. In patients who were not receiving [theophylline](#), serum [alprazolam](#) levels were within the therapeutic range. The authors concluded

that the antagonism of the anxiolytic effects of benzodiazepines by [theophylline](#) may be due to decreased serum benzodiazepine levels in these patients [106].

3.5.1.DG| Thiopental

- 1) Interaction Effect: additive [respiratory depression](#)
- 2) Summary: When used in combination, these drugs may have additive CNS and respiratory depressant effects [144] [145] [146] [147] [148].
- 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 [135] [136] [137] [138] [139].

b) Concomitant administration of intravenous [midazolam](#) and [thiopental](#) resulted in synergistic (supraadditive) effects during [induction of anesthesia](#) [140]. 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 [141]. A 15% reduction in the [thiopental](#) induction dose requirement has been observed if it follows intramuscular premedication with [midazolam](#) [142]. The interaction between [midazolam](#) and [thiopental](#) may in part be dependent on [thiopental](#) dosing [143].

3.5.1.DH| Troleandomycin

- 1) Interaction Effect: increased benzodiazepine toxicity (CNS depression, ataxia, lethargy)
- 2) Summary: Macrolide antibiotics may inhibit hepatic enzymes responsible for benzodiazepine metabolism leading to increased plasma concentrations of benzodiazepines through reduced clearance, prolonged half-life, and increased volume of distribution [92] [93] [94] [95].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Observe patients receiving concurrent macrolide antibiotics and benzodiazepines for enhanced CNS effects. Warn patients regarding potential for drug hangover. Smaller benzodiazepine doses (dose reduction by 50% to 75%) may be required after two to four days of concurrent macrolide antibiotic dosing.
- 7) Probable Mechanism: decreased hepatic metabolism; decreased clearance
- 8) Literature Reports

a) An 8-year-old boy undergoing [adenoidectomy](#) was premedicated with oral [midazolam](#) 0.5 mg/kg and oral [atropine](#) 0.03 mg/kg, followed in 1 hour by [erythromycin](#) 400 mg IV. The patient lost consciousness 40 minutes later after 200 mg had been infused; other vital signs remained normal, and he regained consciousness after 45 minutes. At 170 minutes post-medication, his [midazolam](#) plasma concentration was 134 ng/mL. Six other children who were similarly premedicated

(midazolam 0.5 mg/kg and atropine 0.03 mg/kg) but did not receive erythromycin had a mean midazolam level of 73 ng/mL [89].

b) In a study involving normal volunteers, erythromycin (333 mg TID for 3 days) increased the peak levels of triazolam by 50%, increased the half-life from 4 to 6 hours, and decreased the volume of distribution [90].

c) A double-blind, placebo-controlled study of healthy volunteers has found that clearance of intravenously administered midazolam is reduced by about 50% following 5 days of erythromycin therapy versus placebo [91].

3.5.1.DI] Voriconazole

1) Interaction Effect: increased alprazolam concentrations and potential alprazolam toxicity (excessive sedation and prolonged hypnotic effects)

2) Summary: Concomitant administration of alprazolam and voriconazole is not recommended. Voriconazole has the potential to increase serum concentrations of alprazolam [118]. Because the initial step in alprazolam metabolism is hydroxylation catalyzed by CYP3A and in vitro studies demonstrate the potential for voriconazole to inhibit the CYP3A, voriconazole may have a profound effect on the clearance of alprazolam [164]Q3 [118] [114] [115]. If alprazolam is coadministered with voriconazole, consider reducing the dose of alprazolam and monitor for alprazolam toxicity (excessive sedation, fatigue, ataxia, slurred speech, slowed reactions, and other psychomotor impairment) [164] [118].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent use of alprazolam and voriconazole is not recommended. Concurrent use of alprazolam and voriconazole increases alprazolam concentrations and psychomotor effects. If concurrent use is required, consider reducing the dose of alprazolam and monitor for increased alprazolam toxicity (excessive sedation and prolonged hypnotic effects) [164].

7) Probable Mechanism: inhibition of the P450 3A4 enzyme system-mediated alprazolam metabolism by voriconazole

3.5.1.DJ] 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 [270].

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 [270].

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 [alprazolam](#)
- 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 [278] [279] [280].
- 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 [277].

3.5.2.B) Ethanol

- 1) Interaction Effect: increased sedation
- 2) Summary: Ethanol enhances the adverse psychomotor effects and decreases the ability to do tasks requiring alertness when combined with [alprazolam](#). Acutely, ethanol may inhibit benzodiazepine metabolism, especially in patients with borderline liver disease [273] [274]. Use caution when motor skills are required since ethanol and [alprazolam](#) together can result in additive central nervous system depression [275].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Patients receiving [alprazolam](#) should be advised against ethanol use.
- 7) Probable Mechanism: decreased hepatic clearance of [alprazolam](#)

3.5.2.C) Grapefruit Juice

- 1) Interaction Effect: increased [alprazolam](#) exposure
- 2) Summary: Concurrent use of [alprazolam](#), a CYP3A4 substrate, with grapefruit juice, a CYP3A4 inhibitor, may increase [alprazolam](#) plasma concentrations [61]. In one study, grapefruit juice increased exposure of [alprazolam](#) only in smokers [276]. Encourage patients to avoid grapefruit juice consumption during [alprazolam](#) therapy.
- 3) Severity: major
- 4) Onset: rapid
- 5) Substantiation: probable

6) Clinical Management: Concurrent use of [alprazolam](#) with grapefruit juice may increase [alprazolam](#) plasma concentrations [61]. Encourage patients to avoid grapefruit juice consumption during [alprazolam](#) therapy.

7) Probable Mechanism: inhibition of CYP3A4-mediated [alprazolam](#) metabolism by grapefruit juice

8) Literature Reports

a) No significant interaction occurred when grapefruit juice was taken concomitantly with [alprazolam](#) except in a subgroup of smokers. Two studies were conducted separately. In study 1, healthy males (n=8; 6 subjects were smokers, 10 or more cigarettes/day) were randomized in a two-way crossover manner with an interval of 4 weeks. Two hundred mL of regular strength grapefruit juice or 200 mL of water was given 3 times a day for 10 days to subjects. On the 8th day, subjects received [alprazolam](#) 0.8 mg single dose on an empty stomach. No significant pharmacokinetic alterations occurred except in the 6 smokers (increased AUC 288 nanograms x hr/mL versus 245 nanogram x hr/mL and significantly prolonged $t_{1/2}$ 19.5 hours versus 14.1 hours. In addition, delayed thinking was observed 1 to 2 hours postdose. In study 2, healthy patients (n=11) with anxiety disorders (5 subjects were smokers) were treated with [alprazolam](#) for 2 to 10 weeks to reach steady-state level: 4 patients received 0.4 mg, 4 patients received 0.8 mg, and 3 patients received 1.2 mg twice daily. Seven patients were on flunitrazepam and 5 patients were on sennoside at fixed dose. Two hundred mL of regular strength grapefruit juice was given three times daily for 7 days. As in Study 1, nonsmokers did not have any significant pharmacokinetic alteration but the 5 smokers had significantly higher mean plasma concentration (22.7 nanograms/mL versus 17.8 nanograms/mL). It has been observed that smokers have altered [alprazolam](#) pharmacokinetics which was also true in the presence of grapefruit juice [276].

3.5.4] Drug-Tobacco Combinations

3.5.4.A] Tobacco

1) Interaction Effect: decreased [alprazolam](#) plasma concentrations and efficacy

2) Summary: [Alprazolam](#) plasma concentrations may be decreased up to 50% in smokers compared to non-smokers due to a probable increase in hepatic metabolism. Patients should be advised not to smoke cigarettes. An increase in the [alprazolam](#) dose should be considered for those patients who smoke concurrently with [alprazolam](#) treatment. A decrease in the [alprazolam](#) dose should be considered when a patient treated with [alprazolam](#) stops smoking [15].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: [Alprazolam](#) plasma concentrations may be decreased up to 50% in smokers compared to non-smokers. Consider the need for increased dosing in patients who smoke cigarettes. Be aware of the possible need for a downward dosage adjustment in patients who stop smoking while being treated with [alprazolam](#).

7) Probable Mechanism: increased hepatic metabolism

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) Reduction in intensity and/or frequency of symptoms of anxiety, [panic disorder](#), and/or depression.

B) Toxic

1) Monitor blood counts, urinalysis, and [blood chemistry](#) analyses during chronic therapy [308].

4.2] Patient Instructions

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

[Alprazolam](#)

Treats anxiety and [panic disorder](#).

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 [alprazolam](#) or to similar medicines, are pregnant, or have [narrow-angle glaucoma](#).

How to Use This Medicine:

Tablet, Liquid, Dissolving Tablet, Long Acting Tablet

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

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

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

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.

Throw away any cotton that was in the bottle and reseal it tightly after each use.

Drugs and Foods to Avoid:

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

Do not use this medicine if you are also using [ketoconazole](#) or [itraconazole](#).

Some medicines and foods can affect how [alprazolam](#) works. Tell your doctor if you are using [clarithromycin](#), [cimetidine](#), [cyclosporine](#), [desipramine](#), [diltiazem](#), [ergotamine](#), [erythromycin](#), [fluconazole](#), [fluoxetine](#), [fluvoxamine](#), [imipramine](#), [nefazodone](#), [nicardipine](#), [nifedipine](#), [sertraline](#), [theophylline](#), [birth control pills](#), or seizure medicine.

Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Tell your doctor if you drink alcohol or if you are using any medicine that makes you sleepy, such as allergy medicine or narcotic pain medicine.

Warnings While Using This Medicine:

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

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

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.

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.

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

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

Possible Side Effects While Using This Medicine:

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

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

Blistering, **peeling**, red skin rash

Confusion, problems with coordination or memory

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

Seizure

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

Change in appetite or weight

Constipation

Lightheadedness, drowsiness

Nervousness, restlessness

Loss of interest in sex

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

4.3| Place In Therapy

A|) Anxiety Disorders

1|) **Alprazolam** (immediate-release and orally-disintegrating tablets) is indicated for the management of anxiety disorder or for the short-term relief of anxiety symptoms. Anxiety associated with depression is responsive to **alprazolam**, but **alprazolam** is not meant to treat anxiety or tension due to the stress of everyday life [57] [60]

B|) Depression

1|) Although some studies have indicated that **alprazolam** is effective in treating depression, the drug has not been shown to be superior to tricyclic antidepressants. Furthermore, the lack of a homogenous population of endogenously depressed patients and the diversity of depressive rating scales evaluating different symptomatology may have distorted the results of the studies. The efficacy of **alprazolam** as an antidepressant requires further evaluation [21].

C|) Panic Disorder

1|) **Alprazolam** (extended-release, immediate-release, and orally-disintegrating tablets) is indicated for the treatment of **panic disorder** with or without **agoraphobia**. Long-term efficacy has not been evaluated, so periodically reassess the need for continued treatment for durations longer than 8 weeks [57] [58] [60].

2|) **Alprazolam** has been well studied and appears efficacious in treating multiple dimensions of **panic disorder** in patients without comorbid depression. **Alprazolam** improves intensity and frequency of panic attacks and reduces anticipatory anxiety. Other agents such as serotonin reuptake inhibitors and tricyclic antidepressants may be preferred in patients with associated depression; these agents may, however, have

a slower initial response than benzodiazepines. Comorbid conditions and patient-specific tolerance to drug side effects should be taken into consideration when selecting optimal drug therapy for [panic disorder](#) [28]. See Drug Consult reference: CHEMOTHERAPY AND RADIOTHERAPY TREATMENT GUIDELINES FOR NAUSEA AND VOMITING

4.4] Mechanism of Action / Pharmacology

A] Mechanism of Action

1) [Alprazolam](#) is a benzodiazepine compound structurally similar to [diazepam](#) and exerts its effects by binding to various stereo-specific receptors in the CNS [63] [60] [57] [307] [300]. [Alprazolam](#) possesses anticonvulsant, muscle relaxant, and anxiolytic properties similar to other benzodiazepines [303]. However, [alprazolam](#) differs from classic benzodiazepines by virtue of its triazolo benzodiazepine structure (incorporation of a [triazole](#) ring).

2) [Alprazolam](#) has also been reported to exhibit antidepressant properties, which are not characteristic of conventional benzodiazepine derivatives. The drug has been shown effective in the treatment of many items on the Hamilton depression scale, which are not receptive to other benzodiazepines (depressed mood, guilt and suicide tendencies) [306]. The antidepressant effect of [alprazolam](#) may be related to its ability to significantly increase REM latency, an effect seen with tricyclic antidepressants and monoamine oxidase inhibitors and not with classical benzodiazepines (Bonnett et al, 1981) [300].

4.5] Therapeutic Uses

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

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:

Demonstrated effective in the treatment of alcohol withdrawal

Equivalent to that of [DIAZEPAM](#) or [CHLORDIAZEPOXIDE](#) (Kolin & Linet, 1981; McLendon & Fabre, 1980; McLendon & Fabre, 1979)

3) Adult:

a) In an open study of 20 alcoholic patients, [ALPRAZOLAM](#) had a significant impact on reducing anxiety [25]. Initial doses were 0.5 milligram (mg) two times a day 7 to 10 days after the cessation of alcohol consumption. Medication was titrated until symptoms were controlled. Results were measured throughout the 28-day trial by a series of psychological rating scales. The average daily dose was 2.59 mg/day.

4.5.B] Anxiety

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (immediate-release tablet, orally disintegrating tablet); **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

2) Summary:

Indicated for the treatment of anxiety

May be beneficial for anxiety associated with depression

3) Adult:

a) [ALPRAZOLAM](#) in doses of 0.75 to 3 milligrams daily (in divided doses) has been demonstrated effective in the treatment of [anxiety neurosis](#) in uncontrolled and controlled studies involving in-patients and out-patients [3] [4] [5] [6] [7] [8] [9] [10] [11]. Drowsiness with [ALPRAZOLAM](#) was usually less than that observed with [DIAZEPAM](#), with doses of 1.5 to 2 milligrams [ALPRAZOLAM](#) producing anxiolytic effects equivalent to 18.6 to 28.3 mg [DIAZEPAM](#) daily [8] [6]. [ALPRAZOLAM](#) probably offers no special advantages over other benzodiazepines except possibly when treating anxiety associated with depression.

b) [ALPRAZOLAM](#) 0.5 to 1 milligram orally three times a day was significantly superior to placebo in relieving anxiety symptoms in a controlled study involving 30 hospital outpatients with moderate to severe neurotic anxiety. Results were based on the Hamilton Anxiety Rating Scale and Global Impression Scale [3].

c) [ALPRAZOLAM](#) 1.5 to 3 milligrams (mg) daily was at least as effective as [DIAZEPAM](#) 15 to 30 mg daily as an anxiolytic in a controlled study involving 46 out-patients with moderate to severe anxiety [12]. [ALPRAZOLAM](#) demonstrated antidepressant activity in patients with [neurotic depression](#), whereas no antidepressant effect was observed with [DIAZEPAM](#).

d) The efficacy of [ALPRAZOLAM](#) as compared to placebo in outpatients with anxiety and neurosis was evaluated in a double-blind fashion [7]. Patients were randomly allocated to [ALPRAZOLAM](#) (n=37) 0.25 milligrams (mg) three times a day or placebo (n=25) tablets three times daily for 4 weeks. The dose of [ALPRAZOLAM](#) was titrated upward to a maximum daily dose of 3 mg. Of 46 evaluable patients, the mean daily dose of [ALPRAZOLAM](#) was 1.35 mg (range, 0.75 to 2.25 mg daily). [ALPRAZOLAM](#) was more effective than placebo in 82 of 84 comparisons of anxiety scale scores during the 4-week study. Drop-outs included 13 patients receiving placebo and only 3 receiving [ALPRAZOLAM](#). Side effects with [ALPRAZOLAM](#) were significantly less than placebo, with drowsiness and mucosal dryness being the most commonly reported effects.

e) In a single-blind, crossover study, significant improvement in anxiety and somatic complaints was reported by the 4th day in the majority of patients (n=18) receiving [ALPRAZOLAM](#) 2 milligrams daily as compared to placebo for moderate to severe anxiety with or without depression [11].

f) [ALPRAZOLAM](#) (0.75 to 3 milligrams daily) was reported superior to placebo in the treatment of moderate-to-severe anxiety in chronic schizophrenic outpatients who were stabilized on neuroleptic medication [13]. The mean trial dosage at the end of the 4-week study was 2.4 milligrams/day.

g) **ALPRAZOLAM** was safe, effective, and well tolerated for the treatment of co-morbid [generalized anxiety disorder](#) and [irritable bowel syndrome](#) [14]. Only a limited post-treatment rebound was observed.

4.5.C] Anxiety - [Chronic obstructive pulmonary disease](#)

1) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

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

2) Summary:

May be effective in decreasing anxiety associated with respiratory problems

More studies required to evaluate efficacy and SAFETY

3) Adult:

a) **ALPRAZOLAM** was reported effective in improving levels of anxiety, dyspnea, and subjective feelings (alertness, contentment, calmness) in a 50-year-old anxious patient with [chronic obstructive pulmonary disease](#) (COPD) [38]. **ALPRAZOLAM** given as a single 0.5 milligram test dose did not adversely affect respiratory center output in this patient.

4.5.D] [Behavioral syndrome](#) - [Dementia](#)

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:

As effective as low dose [haloperidol](#) in controlling behavioral episodes in elderly, demented patients

3) Adult:

a) **Alprazolam** was as effective as low-dose [haloperidol](#) in a double-blind, cross-over trial in elderly, nursing home patients with disruptive behaviors associated with [delirium](#), [dementia](#), [amnesic disorders](#), and other [cognitive disorders](#) [34]. Patients (n=48) were currently receiving [haloperidol](#) 1 milligram (mg) or less on a scheduled basis. Behavioral episodes were measured at baseline. Thereafter patients either continued [haloperidol](#) for 6 weeks or entered a 2-week washout period followed by [alprazolam](#) 0.5 mg daily for 4 weeks. Both groups were reassessed and then crossed-over into the other group. There was no significant difference in the number of behavioral episodes for patients taking

alprazolam compared to patients receiving haloperidol. There was also no difference in either group as compared to baseline. Since no placebo was used in this study, it is difficult to determine whether the patients actually benefited from either therapy.

4.5.E] Cancer pain; Adjunct

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:

Case reports have noted efficacy as adjunctive therapy for cancer pain

3) Adult:

a) ALPRAZOLAM was reported effective in the treatment of chronic, organic pain of malignant origin in an uncontrolled study involving 39 patients with various types of cancer [35]. Patients were initially treated for underlying mood or anxiety disorder, and beneficial effects on causalgic pain were unexpected. ALPRAZOLAM was given in doses of 1.5 to 4 milligrams daily in combination with narcotic analgesics, which had been ineffective in controlling causalgic pain syndrome. In addition, improvement in the anxiety disorder was observed in 87% of patients. These data suggest that benzodiazepines may have a place in the treatment of REFRACTORY PAIN in this patient population. The types of cancer observed in this study were hematological (lymphoma), head and neck (squamous cell carcinoma) sarcoma (Ewing's, fibrosarcoma), thoracic (oat cell carcinoma, adenocarcinoma) and breast (intraductal, adenocarcinoma, papillary).

4.5.F] Chemotherapy-induced nausea and vomiting; Prophylaxis

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 preventing ANTICIPATORY NAUSEA,
Not effective in reducing prechemotherapy vomiting, or nausea during and after chemotherapy

3) Adult:

a) ALPRAZOLAM prevented anticipatory nausea in a small controlled study involving 8 patients receiving cancer chemotherapy [36]. The drug was also effective in reducing vomiting during and after

chemotherapy. All 8 patients exhibited previous anxiety related to chemotherapy. [ALPRAZOLAM](#) therapy was initiated at the dinner meal on the evening prior to chemotherapy. The drug was generally given in doses of 0.25 milligrams (mg) at dinner, 0.5 mg at bedtime, 0.5 mg after awakening in the morning, and 1 mg at noon prior to chemotherapy. After chemotherapy, doses of 0.5 mg four times a day were administered for 2 further days. Other antiemetics administered were continued as usual. [ALPRAZOLAM](#) was, however, not effective in reducing prechemotherapy vomiting, or nausea during and after chemotherapy, as compared to placebo.

4.5.G] Chemotherapy-induced nausea and vomiting; Treatment and Prophylaxis

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

4.5.H] Chest pain

1) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

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

2) Summary:

Effective in case reports of atypical chest pain (without evidence of [coronary artery disease](#)) and [panic disorder](#)

3) Adult:

a) [ALPRAZOLAM](#) 1.25 to 6.0 milligrams daily (mean, 3.66 milligrams daily) was reported beneficial in the treatment of cardiology patients with atypical chest pain (without evidence of [coronary artery disease](#)) and [panic disorder](#) in an open study [37]. Significant improvements were observed in panic attack frequency, HAM-A, HAM-D, CGI and SCL-90 anxiety scale with [ALPRAZOLAM](#) treatment.

4.5.I] Depression

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 neurotic and "primary" depression

3) Adult:

a) **ALPRAZOLAM** has been reported effective in the treatment of neurotic and "primary" depression, indicating the drug may not be a classical benzodiazepine and may have pharmacological properties which are efficacious in the treatment of depression [18] [19] [20] [11]. In a comprehensive review of the literature, **ALPRAZOLAM** was noted to be as effective in the treatment of depression as **IMIPRAMINE** [21]. The drug was similar to **IMIPRAMINE** in relieving depression and more effective than **IMIPRAMINE** in relieving somatic symptoms. However, it is suggested that more well-controlled studies are required in patients with the homogenous diagnosis of **endogenous depression** before the relative efficacy of the drug can clearly defined.

b) **ALPRAZOLAM** was as effective in the treatment of primary depression (neurotic and reactive) as **IMIPRAMINE** [19]. In this study, 154 patients were randomly allocated to **ALPRAZOLAM**, **IMIPRAMINE** or placebo for 6 weeks. Mean daily doses of **ALPRAZOLAM** throughout the study were 2.6 milligrams, and mean doses of **IMIPRAMINE** were 128.4 milligrams daily. **ALPRAZOLAM** was associated with less confusion, **tachycardia**, palpitations, and urinary retention (anticholinergic effects) as compared with **IMIPRAMINE**. **IMIPRAMINE** was associated with fewer headaches than **ALPRAZOLAM**. Otherwise, both drugs produced a similar incidence of side effects, including drowsiness, insomnia, nervousness, constipation and light-headedness. The onset of action of **ALPRAZOLAM** was more rapid than **IMIPRAMINE**, with onset of action occurring in the first week of therapy.

c) **ALPRAZOLAM** in doses of 0.5 to 3 milligrams daily was more effective than placebo in a double-blind study involving 462 patients with moderate to severe anxiety for at least 1 month [22]. Side effects were not significantly different between placebo and **ALPRAZOLAM**.

d) In an uncontrolled study, improvement was observed in all psychological ratings in 16 outpatients treated with **ALPRAZOLAM** for **neurotic depression** [20]. Patients were given **ALPRAZOLAM** 0.5 to 1.5 milligrams orally two to three times a day for 21 days (average total dose, 50.4 milligrams). Of 15 patients completing the study, 8 patients improved "very much," 4 patients were "much better", and 3 were "slightly better."

e) In an uncontrolled study, **ALPRAZOLAM** 1.5 to 5 milligrams, daily produced clinical improvement in 13 of 26 inpatients with depression. Their depression was considered severe for at least one month prior to treatment according to the Feighner Depression Checklist, Hamilton Psychiatric Rating Scale for Depression and others [23].

f) **ALPRAZOLAM** 0.25 milligrams orally three times a day in combination with **TRANLYCYPROMINE** (60 to 90 mg daily) was reported effective in the treatment **ATYPICAL DEPRESSION** associated with panic attacks in a 53-year-old male. The patient had not responded adequately to **TRANLYCYPROMINE** alone [24].

4.5.J] Essential tremor

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 essential tremor

Sedation may limit its usefulness

3)) Adult:

a)) [ALPRAZOLAM](#) 0.75 to 2.75 milligrams daily was reported effective in the treatment of essential tremor in a double-blind study involving 24 patients [39]. The most common dose employed was 0.5 mg three times daily. Sedation or drowsiness occurred in 50% of patients treated; however, this was not significantly greater than placebo.

4.5.K) Migraine

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:

May occasionally be useful for migraine headache refractory to other drugs

3)) Adult:

a)) One study reported the benefits of [ALPRAZOLAM](#) 3 milligrams (mg) daily or greater in a 47-year-old woman with [REFRACTORY MIGRAINE HEADACHES](#) [40]. Migraine recurred when doses were tapered below 3 mg daily.

4.5.L) Obsessive-compulsive disorder

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:

Effective in one case report

3)) Adult:

a)) One uncontrolled case report describes the efficacy of [ALPRAZOLAM](#) 1.5 to 12 milligrams daily in the treatment of [obsessive-compulsive disorder](#) in a 30 year old male [41].

4.5.M] Panic disorder, With or without agoraphobia

FDA Labeled Indication

1) Overview

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

2) Summary:

Indicated for the treatment of panic attacks

Notable reductions in panic attacks within the first 2 weeks

3) Adult:

a) **ALPRAZOLAM** has demonstrated efficacy in alleviating panic attacks when used in doses up to 10 milligrams/daily [28] [16]; (Anon, 1992; Chouiard et al, 1983) [29] [30]. **ALPRAZOLAM** was demonstrated as superior to placebo based on "the number of patients with zero panic attacks." Additionally, global improvement scores improved in those receiving **ALPRAZOLAM** compared to placebo [16].

b) In a multicenter, double-blind trial involving 526 patients, **ALPRAZOLAM** 1 to 10 milligrams (mg) daily was reported superior to placebo in the treatment of **agoraphobia with panic attacks** and **PANIC DISORDER** [31]. **ALPRAZOLAM** was superior to placebo at the end of the first week of treatment with regard to phobic fears, spontaneous and situational panic attacks, anxiety, avoidance behavior and secondary disability. At week 4 of treatment, 82% of patients treated with **ALPRAZOLAM** were moderately improved or better as opposed to 43% receiving placebo; 50% of patients treated with **ALPRAZOLAM** were free of panic attacks at this time as compared to 28% of patients treated with placebo. Based upon these data, that authors suggest that, although many patients may respond to 2 mg daily **ALPRAZOLAM**, up to 1/3 of patients may require 6 mg daily for optimal response.

c) In a double-blind study, an 8-month therapy period for **panic disorder** with either **alprazolam** or **imipramine** was effective [28]. Patients received **alprazolam** (n=37), **imipramine** (n=34), or placebo (n=35) during an 8-week period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Patients receiving **alprazolam** began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving **imipramine** began at 25 mg and were increased to 250 mg. **Alprazolam** patients had notable reductions in panic attacks during the first 2 weeks of therapy while **imipramine** patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this time were 11% in the **alprazolam** group, 41% in the **imipramine** group, and 57% in the placebo group (p less than 0.001 for **alprazolam** versus the other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the **alprazolam** and 26% of the **imipramine** groups were panic-free (p less than 0.01). During the follow-up period, patients could be treated with non-study medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be panic-free than those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients,

those with a history of more frequent or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

d) Concomitant **ALPRAZOLAM** (0.5 milligram (mg) orally three times a day) and **PROPRANOLOL** therapy (20 mg orally four times a day) was effective in all 16 patients with panic attacks, relieving panic and anticipatory anxiety within 2 weeks of treatment. Dosages of each drug were lower than the usual effective doses of either agents used alone. The dose of both drugs was increased according to clinical symptoms, with dose ranges of 40 to 160 mg/day **PROPRANOLOL** and 1.5 to 3 mg **ALPRAZOLAM** daily being given within 2 weeks. These data suggest a synergistic effect [32].

4.5.N) Posttraumatic stress disorder

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:

Mixed results obtained

3) Adult:

a) Studies have reported mixed results with the use of **alprazolam** 0.5 to 6 milligrams/day for **posttraumatic stress disorder** (Braun et al, 1990) [42]. There has been some improvement in sleep disturbances, anxiety, irritability and autonomic symptoms. However, other patients have experienced no benefits along with increases in angry outbursts.

4.5.O) Premenstrual syndrome

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 effective for premenstrual symptoms

3) Adult:

a) **ALPRAZOLAM** 0.25 milligram orally three times daily was efficacious in the treatment of symptoms of **premenstrual syndrome** (nervous tension, mood swings, irritability, depression, fatigue)

in a controlled study involving 19 women [43]. **ALPRAZOLAM** was administered from cycle day 20 through the second day of menstruation; at menstruation, the dose of the drug was decreased by 1 tablet daily and was then discontinued.

4.5.P] Schizophrenia

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:

Questionable efficacy

3) Adult:

a) The addition of **ALPRAZOLAM** in incremental doses up to 3.5 to 4 milligrams (mg) daily to a **FLUPHENAZINE** regimen (30 to 40 mg daily) was reported to result in clinical improvement in 2 patients with **schizophrenia**. **ALPRAZOLAM** therapy resulted in substantial improvement in both positive and negative symptoms of **schizophrenia**, by improving **psychosis** and **emotional blunting**. The withdrawal of **ALPRAZOLAM** resulted in exacerbation of psychotic (positive and negative) and affective symptoms [44].

b) Only minimal benefits of adjunctive **ALPRAZOLAM** therapy were found in 4 schizophrenic or schizoaffective patients with negative symptoms [45]. **ALPRAZOLAM** doses were 1 to 3 milligrams daily in 3 patients; up to 5 milligrams daily in 1. Only 1 of the 4 patients responded to **ALPRAZOLAM** therapy.

4.5.Q] Tinnitus

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:

Reduces the loudness of tinnitus

See Drug Consult reference: [DRUG THERAPY OF TINNITUS](#)

3) Adult:

a) In one double-blind, placebo-controlled trial, patients with constant tinnitus were found to have a reduction in the loudness of their tinnitus while taking therapeutic doses of [alprazolam](#) (0.5 to 1.5 milligrams/daily) [46]. Further studies are needed to confirm this finding.

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Abecarnil

4.6.A.1] [Generalized anxiety disorder](#)

a) Although the onset of effect in [alprazolam](#) was earlier, abecarnil was associated with fewer side effects and withdrawal symptoms in a trial involving 192 symptomatic outpatients with [generalized anxiety disorder](#) (GAD) [344]. During the treatment phase both drugs reduced anxiety, measured by the Hamilton Rating Scale for Anxiety (HAM-A), significantly better than did placebo, and in fact response occurred earlier and degree of response in some measures was significantly greater for [alprazolam](#) than for abecarnil. Interestingly, however, following the rapid 1-week tapering of medication, anxiolytic effects in alprazolam-treated patients attenuated significantly more rapidly than those effects in either of the other two groups (p less than 0.001 versus placebo; p less than 0.03 versus abecarnil). This multicenter, placebo-controlled, short-term comparison of abecarnil (3 milligrams/day to 9 mg/day), [alprazolam](#) (1.5 mg/day to 4.5 mg/day), and placebo, with dosages adjusted by investigators for efficacy and side effects, took place over a 4-week, double-blind treatment period and a 1- to 2-week medication-tapering period. Drowsiness, the adverse event reported most frequently in both treatment groups, occurred more frequently (p less than 0.05) in the alprazolam-treated group.

4.6.B] Adinazolam

4.6.B.1] Panic attack

a) Oral adinazolam mesylate 10 to 120 mg/day (mean, 95.5 mg) was as effective as oral [alprazolam](#) 0.5 to 6 mg/day (mean, 3.1 mg) in the treatment of panic attacks or [agoraphobia with panic attacks](#) during a double-blind, cross-over study involving 13 patients [348]. Adverse effects, predominantly drowsiness, occurred to a similar degree with both agents.

4.6.C] Alpidem

4.6.C.1] Withdrawal sign or symptom

a) In a double-blind study 122 patients suffering from general anxiety disorders were randomized to receive either alpidem 50 mg, three times daily, or [alprazolam](#) 0.5 mg three times daily for six weeks. The authors conclude that alpidem is a valid alternative to benzodiazepine anxiolytic therapy because it produces fewer and weaker withdrawal symptoms than [alprazolam](#) and is better tolerated [349].

4.6.D] [Amitriptyline](#)

4.6.D.1] Depression

a) SUMMARY:

[Amitriptyline](#) was more effective than [alprazolam](#) for the treatment of depression

[Alprazolam](#) is associated with fewer adverse effects

b) In a six-week, double-blind parallel study, [amitriptyline](#) was significantly more effective than [alprazolam](#) in treating 43 outpatients with moderate depression. [Amitriptyline](#) produced significantly

more adverse effects. Patients received [amitriptyline](#) (75 to 225 milligrams (mg)/day, mean 115 mg) or [alprazolam](#) (1.5 to 4.5 mg/day, mean 3.2 mg). Several scales were used to assess efficacy (LaPierre et al, 1994).

c) Both drugs showed some advantages when the efficacy of [alprazolam](#) 1 to 3 milligrams (mg)/day was compared to [amitriptyline](#) 50 to 150 mg/day in 104 patients with neurotic or [reactive depression](#). This 4-week, randomized, double-blind study showed both to be equally effective but [amitriptyline](#) showed a more rapid response with a greater number of side effects. Potential advantages in using [alprazolam](#) as an alternative were its low number of side effects (and possibly better compliance) and a wider margin of safety [352].

d) [Amitriptyline](#) 75 to 225 milligrams (mg)/day was more effective for [major depression](#) as compared to [alprazolam](#) 15 to 45 mg/day in 81 outpatients with [major depression](#) in a 6 week, double-blind, parallel study. The group receiving [amitriptyline](#) had a significantly greater response rate if features of retardation, anxiety, and lack of precipitating factors were present, but overall, there was no significant between-group differences. There was a significantly greater incidence of side effects, particularly anticholinergic, in the [amitriptyline](#) group [353].

4.6.E] Bromazepam

4.6.E.1] Generalized anxiety disorder

a) After 14 days of treatment, bromazepam 3 mg twice a day, [alprazolam](#) 0.5 mg twice a day, and etizolam 0.5 mg twice a day all significantly reduced Hamilton's Rating Scale for Anxiety (HRSA) scores in [generalized anxiety disorder](#) patients. HRSA scores continued to decline (p less than 0.001) following two additional weeks of therapy. All three drugs significantly reduced Hamilton's Rating Scale for Depression (HRSD) scores, in the same group, with [alprazolam](#) and etizolam (21.2% and 17.2% reductions respectively) demonstrating larger reductions in HRSD scores than bromazepam (7.1% reduction). No further significant reduction in depression scores were reported following an additional 14 days of therapy. The drugs were well tolerated with no significant differences in reported side effects [314].

4.6.F] Buspirone

1) Adverse Effects

a) In a double-blind study comparing [buspirone](#) (5 milligrams (mg) three times daily (TID)), placebo, and [alprazolam](#) (0.25 mg TID) for 14 days in 60 healthy elderly subjects, [buspirone](#) did not affect reaction time, vigilance, or performance on tests of psychomotor function and memory [336]. However, given that [alprazolam](#) was found to have only marginal effects on vigilance, psychomotor speed, and memory on treatment day 1, and none after 14 days of treatment, it is possible that the exclusion criteria (eg, "significant or uncontrolled" medical illness, use of a variety of CNS depressants, [neurologic disease](#), psychiatric disorders) biased the sample toward persons less likely to exhibit unwanted CNS effects of therapy, and away from persons more likely to receive the drug in clinical practice.

4.6.G] Chlordiazepoxide

4.6.G.1] Alcohol withdrawal syndrome

a) Two controlled studies have demonstrated that [alprazolam](#) is as effective as [chlordiazepoxide](#) and more effective than placebo in the chronic withdrawal period from ethanol [312] [313]. In the most recent study [313], the efficacy and safety of [alprazolam](#) was investigated with [chlordiazepoxide](#) and placebo in 44 alcoholic patients beginning on the 5th day after their last drink. Patients were randomly allocated to [alprazolam](#) 0.5 to 1.5 milligrams (mg) three times daily (TID) (17 patients), [chlordiazepoxide](#) 10 to 30 mg TID (13 patients) or placebo (14 patients). The mean final doses were 2.7 mg [alprazolam](#) and 56.2

mg [chlordiazepoxide](#) daily. Patients were evaluated weekly for a period of 3 weeks. Results of the study indicated that [alprazolam](#) was more effective than placebo and as effective as [chlordiazepoxide](#) in the treatment of patients withdrawing from chronic phase of [alcohol addiction](#).

b) Although [alprazolam](#) has been shown as effective as [chlordiazepoxide](#), no unique advantages are evident.

c) Both [alprazolam](#) and [chlordiazepoxide](#) were effective in controlling acute withdrawal states [337]. Orally administered [alprazolam](#) was compared with [chlordiazepoxide](#) in 100 patients hospitalized for ethanol withdrawal. However, [alprazolam](#) kinetics and potential antidepressant effects may be more advantageous than [chlordiazepoxide](#).

4.6.H] Clobazam

4.6.H.1] Anxiety

a) There were no significant differences between [alprazolam](#) and clobazam in the treatment of anxiety, but [alprazolam](#) produced consistently better outcomes over placebo in a double-blind trial [311].

4.6.I] Clonazepam

4.6.I.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) [351].

4.6.J] Clonidine

4.6.J.1] Nicotine withdrawal

a) Although [CLONIDINE](#) appears to be effective in promoting smoking cessation, the high incidence of side effects may limit its usefulness [350].

4.6.K] Diazepam

4.6.K.1] Alcohol withdrawal syndrome

a) [Alprazolam](#) has been demonstrated as effective as [diazepam](#) in the management of chronic alcohol withdrawal, but it offers no specific advantages [355]. The efficacy and safety of [alprazolam](#) was compared with [diazepam](#) in 46 alcoholics in double-blind fashion. Both drugs were administered randomly for 21 days beginning on the 5th day after the last drink. The mean optimal daily dose of [alprazolam](#) was 2.2 milligrams (range 1.5 to 4.5 mg/d) and [diazepam](#) 20.2 milligrams (range 15 to 45 mg/d). Based on Hamilton anxiety scores, global scores and other test procedures, both drugs produced significant clinical improvement in 95% of patients in both groups, with no significant difference between the drugs at any time. Both drugs produced frequent drowsiness and lightheadedness with the only difference in side effects being a higher incidence of depression in patients receiving [alprazolam](#) (6 patients as compared to 1 receiving [diazepam](#)). Although the drug has been shown to be as effective as [diazepam](#) in the treatment of alcohol withdrawal, it offers no specific advantages [355].

4.6.K.2] Anxiety

a) Controlled studies have reported that [alprazolam](#) is at least as effective as [diazepam](#) in the treatment of outpatients with anxiety [356] [357] [358] [359] [360]. The incidence of sedation was lower with [alprazolam](#) in some reports (Rickels, 1983a) [358] [359].

b) [Alprazolam](#) 1.5 to 3 milligrams daily was at least as effective as [diazepam](#) 15 to 30 milligrams daily as an anxiolytic in a controlled study involving 46 outpatients with moderate to severe anxiety. [Alprazolam](#) demonstrated antidepressant activity in [neurotic depression](#), whereas no antidepressant effect was observed with [diazepam](#) [356].

c) [Alprazolam](#) was compared with [diazepam](#) and placebo in 235 outpatients with anxiety in a 28-day double-blind study [359]. [Alprazolam](#) in mean doses of 1.5 milligrams orally daily was reported as effective as [diazepam](#) 18.6 milligrams (mean) orally daily in this study. [Alprazolam](#) was reported to produce a markedly lower incidence of side effects than [diazepam](#) or placebo, particularly drowsiness. Depression and lightheadedness was reported with both drugs, although less frequently in patients receiving [alprazolam](#). In this study, a detailed description of side effects was not provided, making evaluation of these 2 drugs difficult.

4.6.K.3] [Panic disorder](#)

a) The tolerability and efficacy of [diazepam](#) and [alprazolam](#) was compared over 8 weeks using a double-blind, placebo controlled study with 24 subjects. They found that on all measures of efficacy both agents showed equally favorable results. Despite some sedation during the early part of the trials, both drugs were tolerated well [361].

4.6.L] [Etizolam](#)

4.6.L.1] [Anxiety](#)

a) In three double-blind, randomized trials, oral etizolam and [alprazolam](#), both at 0.5 milligram twice daily for 4 to 5 weeks, showed comparable therapeutic effect in the treatment of [generalized anxiety disorders](#). Both drugs produced a statistically significant improvement in anxiety and depression symptoms rated according to Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale. Apart from a few cases of moderate daytime sedation, both drugs were well tolerated, without significant differences in adverse effects between treatments [338] [339] [340].

4.6.L.2] [Panic disorder](#)

a) In a randomized, double-blind, placebo-controlled study of 30 patients, etizolam 0.5 milligram (mg) twice a day was as effective as [alprazolam](#) 0.5 mg twice a day in the treatment of [panic disorders](#) associated with [agoraphobia](#). Both drugs were well tolerated. More extensive and longer studies are needed to confirm these results [341].

4.6.M] [Haloperidol](#)

4.6.M.1] [Dementia](#) - Problem behavior

a) [Alprazolam](#) was as effective as low-dose [haloperidol](#) in a double-blind, cross-over trial in elderly, nursing home patients with disruptive behaviors associated with [delirium](#), [dementia](#), [amnesic disorders](#), and other [cognitive disorders](#) [362]. Patients (n=48) currently receiving [haloperidol](#) 1 milligram (mg) or less on a scheduled basis had behavioral episodes measured at baseline. Thereafter patients either continued [haloperidol](#) for 6 weeks or entered a 2-week washout period followed by [alprazolam](#) 0.5 mg daily for 4 weeks. Both groups were reassessed and then crossed-over into the other group. There was no significant difference in the number of behavioral episodes for patients taking [alprazolam](#) compared to patients receiving [haloperidol](#). There was also no difference in either group as compared to baseline. Since no placebo was used in this study, it is difficult to determine whether the patients actually benefited from either therapy.

4.6.N] Hydroxyzine

4.6.N.1] Administration of medication, Premedication - Preoperative care

a) [Alprazolam](#) and [hydroxyzine](#) were compared in a double-blind controlled study as surgical premedicants [354]. In terms of anxiolytic and adverse effects, [alprazolam](#) was found to be the preferred agent.

4.6.O] Imipramine

4.6.O.1] Anxiety

a) A six-week, double-blind, parallel study was conducted in 60 patients with [generalized anxiety disorder](#) to evaluate the efficacy of [alprazolam](#) and [imipramine](#) [333]. After a three-week washout period, patients were equally divided and randomly assigned to [alprazolam](#) 0.5 milligram or [imipramine](#) 25 milligrams three times daily for six-weeks. After the first week the dose of the medication could be increased by one capsule daily up to a maximum of 12 capsules per day. At the end of the study the average dose was for the [alprazolam](#)-treated group was 2.2 mg/day (0.5 to 6 mg/day) and for the [imipramine](#) group 91 mg/day (25 to 200 mg/day). During the first two weeks, [alprazolam](#) was superior to [imipramine](#). After two weeks both drugs were effective based on psychic and somatic parameters, but [imipramine](#) predominantly affected psychic symptoms (eg, negative anticipatory thinking and [dysphoria](#)) as [alprazolam](#) was superior in attenuating somatic symptoms.

b) [Alprazolam](#) and [imipramine](#) might be useful in the treatment of school refusal ([school phobia](#)); however, further clinical trials need to be conducted to document their usefulness [334].

4.6.O.2] Depression

a) [Alprazolam](#) was as effective as [imipramine](#) in the treatment of primary depression [315]. The mean effective doses of [alprazolam](#) in the study were 2.6 milligrams daily in divided doses, as compared with 128.4 milligrams daily for [imipramine](#). The onset of action with [alprazolam](#) was more rapid than that observed with [imipramine](#); antidepressant effects were more evident with [alprazolam](#) during the first week of therapy. A similar incidence of side effects occurred with each medication, with the main side effects being drowsiness, insomnia, nervousness, constipation and lightheadedness. However, [alprazolam](#) was reported to have less anticholinergic side effects (confusion, [tachycardia](#), palpitations, dry mouth, urinary retention). [Imipramine](#) was reported to cause fewer headaches than [alprazolam](#). However, a detailed description of side effects in these patients was not provided in this study. In addition, specific data regarding the onset of effects of each medication were also not provided satisfactorily. More importantly, the patient population ("primary" depression) is unclear in this study. It is difficult to evaluate which types of depression were being treated.

b) [Alprazolam](#) was compared with [imipramine](#) in a 6-week, double-blind study on 723 outpatients [316]. Patients were selected with moderate to severe symptoms of a unipolar [major depressive disorder](#) of at least one month duration. Patients were given [imipramine](#) 25 milligrams two or three times daily or [alprazolam](#) 0.5 milligram two to three times daily initially, followed by increases in doses at one-week intervals to a maximum of 4.5 mg [alprazolam](#) and 225 mg [imipramine](#) daily. Both drugs were more effective than placebo in alleviating depression, with [alprazolam](#) being at least as effective as [imipramine](#). [Alprazolam](#) was reported more effective in relieving somatic symptoms and the data suggested an earlier onset of effect in some evaluated parameters, but the significance of this is questionable. Toxicity, primarily anticholinergic side effects, was reported in patients receiving [imipramine](#); drowsiness was the main side effect reported with [alprazolam](#). This study suggests benefits of [alprazolam](#) in the treatment of [unipolar depression](#) as defined by the Feighner Diagnostic Criteria for primary depression (similar to the DMS-

III Criteria for [major depression](#)). However, this study was performed on an outpatient basis, and even the best blinding techniques are useless if patients are taking other medications. The authors indicate that other psychotropic medications were not to be used except for "emergencies". Evaluation of drug response in depression is difficult at best, especially on an outpatient basis with several investigators doing the evaluation. [Alprazolam](#) may exhibit antidepressant effects.

c) [Alprazolam](#), [imipramine](#), and a placebo were compared in a 6-week, double-blind study of 175 patients with [major depressive disorder](#) (DSM-III) [317]. Patients were randomly assigned to [alprazolam](#) (N=58), [imipramine](#) (N=60) or placebo (N=57) therapy. Dosage increases were allowed during the course of treatment and the mean dosage of [alprazolam](#) and [imipramine](#) during the last 2 weeks of treatment were 3 milligrams/day and 150 milligrams/day, respectively. Study results indicate that [alprazolam](#) was more effective than [imipramine](#) and placebo therapy. However it should be noted that a high placebo response rate was observed at 2 weeks (53% compared to 75% for [alprazolam](#) and 64% for [imipramine](#)). The high placebo response rate may be attributed to the fact that a high percentage of the patient were of the anxious and [agitated depression](#) subtypes. (Note: The data supplied in the figure comparing clinical improvement over time on the various forms of drug therapy is for 171 different patients, which is interesting since only 153 patients completed at least 4 weeks of treatment. No information is supplied regarding the study dropouts other than the fact that the dropout rates were not significantly different between the 3 treatment groups.) [Imipramine](#) therapy was associated with a higher incidence of drowsiness and dry mouth than [alprazolam](#) or placebo therapy.

d) The efficacy of [alprazolam](#) and [imipramine](#) were evaluated in the inpatient treatment of [depressive illness](#) [318]. Patients were randomly assigned to either [alprazolam](#) or [imipramine](#) therapy. Dosage was individualized to patient response. Patients receiving [alprazolam](#) therapy improved over the first 10 days of therapy and then reached a plateau, whereas the patients treated with [imipramine](#) continued to improve in vegetative and cognitive symptomology. Further examination of the HAM-D scale indicated that the initial improvements seen with [alprazolam](#) is predominantly related to the vegetative features of the illness.

e) Both drugs administered once daily were efficacious in the treatment of outpatients with [major depressive disorders](#) [319]. Fifty percent of the [alprazolam](#) treatment group had a greater than 50% improvement in their HAM-D scores, compared to the 38% success rate observed in the [imipramine](#) treatment group and 18% in the placebo treatment groups.

f) Patients who can be classified as DSM-III - [major depressive episode](#) but fail to satisfy more restrictive criteria for primary depression disorder appear to respond better to [alprazolam](#) therapy than [imipramine](#) therapy. Patients satisfying the stricter criteria for primary depression also appear to tolerate and respond better to [alprazolam](#) therapy initially. However, [imipramine](#) appeared to be more efficacious during long term therapy. In addition, patients with biologic depression (eg, melancholic, positive DST, and shortened REM latency) tended to respond better to [imipramine](#) therapy [320].

g) An 8-week, double-blind, controlled study compared the efficacy of [alprazolam](#) (58 patients), [diazepam](#) (59 patients), [imipramine](#) (63 patients), and placebo (61 patients) in 241 outpatients with a DSM-III diagnosis of [major depression](#). Week 1 was a washout period with all patients receiving placebo. Week 2 through 7, the patients received their assigned medication, and during week 8 the dose of the medication was reduced by half for 3 days and discontinued for the remaining 4 days. At the end of the study the mean daily doses were 143 milligrams [imipramine](#), 3.1 milligrams [alprazolam](#), 24 milligrams [diazepam](#), and 6.8 capsules of placebo. Attrition rates were significant, 23% by week 4 of treatment and 39% by week 6. By the completion of the study, 41% of the [imipramine](#) group had withdrawn, 23% of the [alprazolam](#) group, 44% of the [diazepam](#) group, and 40% of the placebo group. The main reason given for attrition was side effects with the active compounds and ineffectiveness with placebo. [Alprazolam](#) and [imipramine](#) were both significantly better than placebo in treating depression, but [diazepam](#) was not effective. The clinical effects of [imipramine](#) and [alprazolam](#) were equivalent, and overall the frequency of side effects was similar. [Imipramine](#) produced less drowsiness and more anticholinergic effects than both [alprazolam](#) and [diazepam](#) [321].

4.6.O.3] Panic disorder

a) Summary: [Alprazolam](#) and [imipramine](#) appear to be equally efficacious in the treatment of [panic disorder](#) in most patients. The onset of action is faster with [alprazolam](#), but by the end of four weeks their effectiveness is similar (Rickels & Schweizer, 1998) [322] [323] [324] [325] [326] [327] [328]. The decision to use [imipramine](#) over [alprazolam](#) should be based on patient-related characteristics (eg, concurrent depression, anxiety disorders, [cardiovascular disease](#)), potential drug interactions, and side effects.

b) In a double-blind study, an 8-month therapy period for [panic disorder](#) with either [alprazolam](#) or [imipramine](#) was effective (Rickels & Schweizer, 1998). Patients received [alprazolam](#) (n=37), [imipramine](#) (n=34), or placebo (n=35) during an 8-week period of short-term treatment, a 6-month maintenance period, and then a 15-month follow-up period. Patients receiving [alprazolam](#) began at 1 milligram (mg) daily and were titrated up to 10 mg. Those receiving [imipramine](#) began at 25 mg and were increased to 250 mg. [Alprazolam](#) patients had notable reductions in panic attacks during the first 2 weeks of therapy while [imipramine](#) patients showed improvement over placebo patients after 3 to 4 weeks. Drop-out rates during this time were 11% in the [alprazolam](#) group, 41% in the [imipramine](#) group, and 57% in the placebo group (p less than 0.001 for [alprazolam](#) versus the other groups). In the remaining patients it was noted that tolerance developed to adverse effects during the maintenance phase. After the 6-month maintenance phase, doses were titrated off over 3 weeks. At this point, 62% of the [alprazolam](#) and 26% of the [imipramine](#) groups were panic-free (p less than 0.01). During the follow-up period, patients could be treated with non-study medications. Regardless of medication, patients who completed 8 months of treatment were more likely to be panic-free than those who had dropped out, even if they received non-study medications (85% versus 55%, p less than 0.01). Remission rates were higher in younger patients, those with a history of more frequent or intense panic attacks, those with a lower initial phobia score, and those with an initial lower score of inadequacy, low self-confidence, and passivity (Minnesota Multiphasic Personality Inventory Dependency Scale).

c) Seventy-nine patients were enrolled in a placebo controlled, double-blind trial comparing the efficacy and cardiovascular effects of [imipramine](#), [alprazolam](#), and placebo in patients with [panic disorders](#) [322]. Doses ranges were [alprazolam](#) 1 to 8 milligrams/day and [imipramine](#) 30 to 270 milligrams/day. In terms of global improvement, the patients treated with [alprazolam](#) or [imipramine](#) experienced significantly greater improvement than the placebo patients. [Alprazolam](#) had a more rapid onset of effect, but after four weeks of therapy no significant differences in efficacy were apparent between the [alprazolam](#) and [imipramine](#) treated patients. [Imipramine](#) did have a number of significant effects on the cardiovascular system, however, as the heart rate was significantly increased at resting and standing, and the systolic and diastolic blood pressures were raised.

d) Cerebrospinal fluid levels of homovanillic acid, 5-hydroxyindoleacetic acid, 3-methoxy-4-hydroxyphenylglycol, and somatostatin and beta-endorphin were measured in 12 patients with [panic disorders](#) who had been treated with [alprazolam](#) or [imipramine](#) for seven months. Seven patients treated with [alprazolam](#) (mean dose 4.7 mg, range 2 to 6 mg) all benefited from therapy. Four of the five [imipramine](#)-treated patients (mean dose 135 mg, range 100 to 150 mg) benefited. Cerebrospinal fluid levels of the monoamine metabolites and neuropeptides remained unchanged during therapy in both treatment groups, and were similar to levels measured in a control group, suggesting the antipanic activities of [alprazolam](#) and [imipramine](#) do not involve the monoamine or neuropeptide systems as was previously believed [329].

e) A double-blind, placebo-controlled trial comparing the effects of [imipramine](#) and [alprazolam](#) in patients with [panic disorders](#) revealed both agents were significantly more effective than placebo, however the patients treated with [alprazolam](#) reported less fear than the patients in the [imipramine](#) and placebo groups after eight weeks of therapy [322].

f) The Cross-National Collaborative Panic Study compared [alprazolam](#), [imipramine](#), and placebo in the treatment of [panic disorder](#) [325]. The study used in this evaluation was a double-blind, placebo-

controlled, multicenter system enrolling 1168 patients with a diagnosis of [panic disorder](#) based on DSM-III criteria. Prior to the start of drug treatment all CNS active drugs were discontinued during a one- to two-week washout period. Patients were then randomly assigned to treatment with [alprazolam](#) 1 milligram, [imipramine](#) 25 milligrams, or placebo (1 tablet). The initial starting dose was increased steadily to 6 mg [alprazolam](#), 150 mg [imipramine](#), and 6 placebo tablets by day 19. Subsequently the dosage could be adjusted based on clinical response. Formal psychotherapy and [behavioral treatment](#) sessions were to be avoided during the eight week treatment phase. Efficacy was assessed by using global improvement scores, a panic attack scale, phobia scale, frequency of anticipatory anxiety, 14-item Hamilton Rating Scale for Anxiety, 21-item Hamilton Rating scale for Depression, and Hopkins SCL-90 patient self-rating scale. The treatment-cohort (anyone completing three weeks of therapy) consisted of 1010 patients and 812 patients completed the entire eight-week study. Reasons for dropping-out were side effects ([alprazolam](#) 3.4%, [imipramine](#) 5.9%, and placebo 3.1%), lack of efficacy ([alprazolam](#) 3.1%, [imipramine](#) 2.6%, and placebo 12.8%), treatment refusal (16.1%), and other reasons ([alprazolam](#) 7%, [imipramine](#) 7.7%, and placebo 11.8%); percentage are expressed as the number of patients affected divided by number of patients enrolled in that treatment group. Onset of therapeutic benefits was noted by week 1 and 2 with [alprazolam](#) and week 4 with [imipramine](#). By week 8 there was no difference between the [alprazolam](#) and [imipramine](#) groups and both groups were statistically superior to placebo.

g) [Alprazolam](#) was more effective than [imipramine](#) and placebo on anticipatory anxiety and phobic symptoms in a Scandinavian multicenter study in 41 patients with [panic disorder](#) [330]. [Alprazolam](#) had a more rapid onset of action than [imipramine](#) on all symptoms. Patients receiving [alprazolam](#) had more drowsiness and those receiving [imipramine](#) had more anticholinergic effects.

h) In a study of 123 Scandinavian patients with [panic disorder](#), [alprazolam](#) had an early effect on variables relating to panic attacks, such as severity of spontaneous attacks and avoidance, whereas [imipramine](#) showed a more delayed effect on global measures [331].

i) Patients with mild-to-moderate depression and [panic disorder](#) will respond equally to either [alprazolam](#) (avg dose = 5.25 milligrams/day) or [imipramine](#) (avg dose = 159 milligrams/day) therapy. Both drugs are more effective than placebo in the treatment of patients with mild-to-moderate depression and [panic disorder](#) [332].

4.6.P] Methaqualone

1) Adverse Effects

a) Methaqualone was determined to be more euphoriant than [alprazolam](#), [lorazepam](#), and [diazepam](#) compared with placebo as determined by the Addiction Research Center Inventory and 2 other scales designed to assess abuse potential and sedative intoxication in 30 recreational drug users of college age [346]. The randomized, double-blind study was carried out over a 5-week period with all volunteers receiving single doses of [alprazolam](#) 2 mg, [lorazepam](#) 4 mg, methaqualone 300 mg, [diazepam](#) 20 mg, and placebo. At 1 hour after drug administration, methaqualone produced significantly more euphoria than [alprazolam](#) or placebo. [Diazepam](#) and [lorazepam](#) were more euphoriant than placebo, but not significantly less than methaqualone; however, at 2 hours methaqualone alone was shown to be significantly more euphoric than any other treatment, none of which differed from placebo. The sedation caused by methaqualone was less than that of [alprazolam](#), [lorazepam](#), and [diazepam](#).

4.6.Q] Metoclopramide

4.6.Q.1] Chemotherapy-induced nausea and vomiting - Cisplatin adverse reaction

a) The addition of [alprazolam](#) to [metoclopramide](#) plus [methylprednisolone](#) was evaluated for the control of cisplatin-induced emesis. Alprazolam 0.4 milligram (mg) (PO 3 times a day for 7 days) with [metoclopramide](#) 3 mg/kg/day (IV continuous infusion for 120 hours) plus [methylprednisolone](#) 125 mg (IV

bolus every 8 hours for 5 days) starting on the first day of chemotherapy significantly reduced nausea and vomiting episode over placebo with [metoclopramide](#) plus [methylprednisolone](#) [335].

4.6.R] [Oxazepam](#)

4.6.R.1] Anxiety

a) [Oxazepam](#) (up to 90 milligrams daily) was reported similarly effective as [alprazolam](#) (up to 3 milligrams daily) in the treatment of anxiety in a randomized, double-blind study involving 60 outpatients [345].

4.6.S] [Pregabalin](#)

4.6.S.1] [Generalized anxiety disorder](#)

a) In a manufacturer-sponsored, placebo-controlled study (n=455), pregabalin 300 to 600 milligrams (mg) daily was reported at least as effective as [alprazolam](#) 1.5 mg daily in treating patients with moderate or severe [generalized anxiety disorder](#) [343]. However, this conclusion cannot be confirmed based on data presented. At 4 weeks, both drugs improved anxiety symptoms (Hamilton Anxiety Rating Scale (HAM-A)) to a significantly greater degree than placebo, but efficacy differences between pregabalin and [alprazolam](#) were not provided. Although pregabalin appeared to have a faster onset, lack of specific data preclude adequate assessment of this parameter.

4.6.T] [Propranolol](#)

4.6.T.1] Panic attack

a) [Alprazolam](#) was more effective than [propranolol](#) in reducing panic attacks in patients with [panic disorder](#) and [agoraphobia](#) in a 5-week, double-blind study [309]. [Alprazolam](#) in mean oral doses of 3.62 mg/day was superior to oral [propranolol](#) in mean doses of 185 mg/day in totally eliminating panic attacks. [Alprazolam](#) also produced more improvement than [propranolol](#) on the Assessor Phobia Avoidance Scale. However, [alprazolam](#) was not significantly superior to placebo in reducing panic attacks to zero in this study; the difference between [propranolol](#) and placebo also did not reach significance. This trial does, however, provide evidence that [alprazolam](#) is effective for patients with panic attacks and [agoraphobia with panic attacks](#), and also suggests a relative lack of efficacy of [propranolol](#).

b) A mean daily dose of 5.0 +/- 2.3 mg of [alprazolam](#) or 182.0 +/- 66.5 mg of [propranolol](#) was found [310] to be effective in suppressing panic attacks and reducing avoidance behavior. However, the panicolytic effect of [alprazolam](#) has a more rapid onset of action.

4.6.U] [Tandospirone](#)

1) Efficacy

a) Preliminary data indicate that tandospirone has less potential for abuse and adverse effects on psychomotor performance than [alprazolam](#). In a double-blind crossover study, the behavioral effects and abuse liability of tandospirone and [alprazolam](#) were compared in 14 male volunteers with a history of [sedative abuse](#). Subjects participated in a single-blind session with tandospirone 160 milligrams with behavioral and subjective measures, followed by a double-blind dose-effect phase with tandospirone 40, 80, and 160 mg, [alprazolam](#) 0.5, 1, and 2 mg or placebo. Compared with placebo, [alprazolam](#), but not tandospirone, impaired psychomotor performance. [Alprazolam](#) produced significant dose-related increases in subject-rated drug liking, in contrast to tandospirone which produced significant increases in subject-rated drug disliking [342].

4.6.V] Tropisetron

4.6.V.1] Chemotherapy-induced nausea and vomiting

a) In chemotherapy-naïve breast cancer patients (n=50), the combination of TROPISETRON with ALPRAZOLAM or DEXAMETHASONE was generally more effective than TROPISETRON alone for treatment of nausea and vomiting associated with CEF chemotherapy, although in the patients without stress, tropisetron alone was satisfactory. CEF therapy (cyclophosphamide 600 milligrams/square meter (mg/m²), epirubicin 80 mg/m², and 5-fluorouracil 600 mg/m²) was administered in one day, with the cycle repeated every 21 days. Study medications were given over 3 cycles, and each subject was her own control through the 3 cycles. In the first cycle, all participants received intravenous (IV) tropisetron 5 mg prior to chemotherapy, followed by 3 days of oral tropisetron 5 mg. For the second cycle, IV tropisetron 5 mg and IV dexamethasone 8 mg were given before chemotherapy, followed by 3 days of the same doses of tropisetron and dexamethasone, both orally. For cycle 3, IV tropisetron 5 mg before chemotherapy was combined with oral alprazolam 0.25 mg starting 12 hours (hr) before chemotherapy and continued every 12 hr for 3 days (with tropisetron 5 mg orally for 3 days). Severity ratings for both nausea and vomiting were significantly lower with alprazolam combination therapy compared to tropisetron monotherapy (p=0.001); ratings were marginally lower for the dexamethasone combination over tropisetron alone (p=0.05). Retching was marginally improved with combination treatment (p=0.054). With respect to delayed emesis, both combinations were superior to tropisetron alone (p less than 0.001) and showed equivalent efficacy. When the cohort was stratified for presence of stress (based on the Hamilton scale), there was no significant difference between the 3 protocols for women with low levels of stress (scores below 20), while those with more stress (scores above 20) did significantly better on the combination protocols (p less than 0.001). The side effect of sedation was greater when alprazolam was used; headache worsened with tropisetron alone; appetite was better with either combination [347].

6.0] References

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