

DRUGDEX-EV 0362

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ZOLPIDEM

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0.0] Overview

1] Class

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

Nonbarbiturate Hypnotic

2] Dosing Information

a)] [Zolpidem](#) Tartrate

1] Adult

a)] Insomnia, Characterized by difficulty returning to sleep after middle-of-the-night awakening

1)] SL tablet, Intermezzo(R), 1.75 mg SL for women and 3.5 mg SL for men (MAX dose) taken only once per night [1]

b)] Insomnia, Short-term treatment

1)] immediate-release tablet, Ambien(R) (men), initial, 5 or 10 mg ORALLY immediately before bedtime; MAX 10 mg/day; use lowest dose possible [11]

2)] immediate-release tablet, Ambien(R) (women), initial, 5 mg ORALLY immediately before bedtime; may increase to MAX 10 mg/day; use the lowest dose possible [11]

3)] extended-release tablet, Ambien CR(R) (men), initial, 6.25 or 12.5 mg ORALLY immediately before bedtime; MAX 12.5 mg/day; use lowest dose possible [12]

4)] extended-release tablet, Ambien CR(R) (women), initial, 6.25 mg ORALLY immediately before bedtime; may increase to MAX 12.5 mg/day; use the lowest dose possible [12]

5)) oral spray, Zolpimist(R) (men), 5 or 10 mg (1 or 2 sprays directly into mouth over the tongue) ORALLY immediately before bedtime; MAX 10 mg/day [13]; use lowest dose possible [14]

6)) oral spray, Zolpimist(R) (women), 5 mg (1 spray directly into mouth over the tongue) ORALLY immediately before bedtime [14]

7)) SL tablet, Edluar(R) (men), 5 or 10 mg SL immediately before bedtime; MAX 10 mg/day; use lowest dose possible [15]

8)) SL tablet, Edluar(R) (women), 5 mg SL immediately before bedtime; may increase to MAX 10 mg/day; use lowest dose possible [15]

2)) Pediatric

a)) safety and efficacy in pediatric patients have not been established [15] [11] [12] [1] [13]

3)) Contraindications

a)) Zolpidem Tartrate

1)) hypersensitivity to zolpidem tartrate [15] [12] [11] [1] [13]

4)) Serious Adverse Effects

a)) Zolpidem Tartrate

1)) Anaphylaxis

2)) Angioedema

3)) Chest pain

4)) Complex mannerisms - behavior

5)) Depression, worsening

6)) Hepatic encephalopathy

7)) Suicidal thoughts

8)) Tachycardia

5)) Clinical Applications

a)) Zolpidem Tartrate

1)) FDA Approved Indications

a)) Insomnia, Characterized by difficulty returning to sleep after middle-of-the-night awakening

b)) Insomnia, Short-term treatment

1.0] Dosing Information

[Drug Properties](#)

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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

[Zolpidem](#)

[Zolpidem](#) Tartrate

C)) Physicochemical Properties

1)) [Zolpidem](#) Tartrate

a)) Molecular Weight

1)) 764.88 [33]

b)) pKa

1)) 6.16 [175]

c)) Solubility

1)) Sparingly soluble in water, alcohol, and propylene glycol [33].

1.2] Storage and Stability

A)) [Zolpidem](#) Tartrate

1)) Preparation

a)) Oral route

1)) Oral Spray

a)) To prime the pump, spray 5 times (prime with 1 spray if not used for at least 14 days). To administer, hold the pump upright, point the black spray opening directly in mouth, and fully press down the pump (5 mg/each spray). For faster sleep onset, do not administer with or immediately after a meal [13].

2)) Immediate-Release Tablets

a)) Administration with or immediately after a meal may delay onset of action [11].

3j) Extended-Release Tablets

a) Extended-release zolpidem tablets should be swallowed whole. Do not divide, crush, or chew tablets. Administration with or immediately after a meal may delay onset of action [12].

b) Sublingual route

1) SL zolpidem tablets should be placed under the tongue and allowed to dissolve. Do not swallow whole or take with water. Zolpidem SL tablets should not be administered with or immediately after a meal as this may delay onset of action [15] [1].

B) Zolpidem Tartrate**1) Oral route****a) Spray/Tablet/Tablet, Extended Release**

1) Store oral spray upright at a controlled room temperature of 25 degrees C (77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Avoid prolonged exposure to temperatures above 30 degrees C (86 degrees F). Do not freeze [13].

2) Store extended-release tablets between 15 and 25 degrees C (59 and 77 degrees F), with limited excursions permitted up to 30 degrees C (86 degrees F) [139].

3) Store immediate-release tablets at a controlled room temperature of 20 to 25 degrees C (68 to 77 degrees F) [33].

2) Sublingual route**a) Tablet**

1) Store at a controlled room temperature of 20 to 25 degrees C (68 to 77 degrees F); protect from light and moisture [34].

2) Store between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F); protect from moisture [1].

1.3] Adult Dosage**1.3.1] Normal Dosage****1.3.1.A] Zolpidem Tartrate****1.3.1.A.1] Oral route****1.3.1.A.1.a] Insomnia, Short-term treatment****1) Oral Spray (Zolpimist(R))**

a) For the treatment of insomnia, the usual dose of [zolpidem](#) oral spray in men is 5 or 10 mg (1 or 2 sprays) directly into mouth over the tongue, immediately before bedtime. The maximum dose is 10 mg/day [13]. The lowest effective dose should be used. The recommended dose in women is 5 mg (1 spray) directly into mouth over the tongue, immediately before bedtime [14].

2) Immediate-Release Tablets ([Ambien\(R\)](#))

a) For the treatment of insomnia, the recommended starting dose of [zolpidem](#) oral immediate-release tablets is 5 or 10 mg in men and 5 mg in women, given only once daily, immediately before bedtime and when at least 7 to 8 hours remain before the planned time of awakening. The dose should be individualized, using the lowest effective dose. Total dose should not exceed 10 mg/day. If insomnia fails to respond to [zolpidem](#) within 7 to 10 days, reevaluate patient for an underlying primary psychiatric or physical condition [11].

3) Extended-Release Tablets ([Ambien CR\(R\)](#))

a) The recommended starting dose of [zolpidem](#) for the treatment of insomnia is 6.25 or 12.5 mg in men and 6.25 mg in women, given only once daily, immediately before bedtime and when at least 7 to 8 hours remain before the planned time of awakening. The dose should be individualized, using the lowest effective dose. Total dose should not exceed 12.5 mg/day. If insomnia fails to respond to [zolpidem](#) within 7 to 10 days, reevaluate patient for an underlying primary psychiatric or physical condition [12]

1.3.1.A.2] Sublingual route

1.3.1.A.2.a] Insomnia, Characterized by difficulty returning to sleep after middle-of-the-night awakening

1) The recommended and maximum dose of [zolpidem](#) tartrate SL tablet is 1.75 mg for women and 3.5 mg for men. The tablet should be taken only once per night as needed if a middle-of-the-night awakening is followed by difficulty returning to sleep [1].

1.3.1.A.2.b] Insomnia, Short-term treatment

1) For the short-term treatment of insomnia, with [difficulties in sleep initiation](#), the recommended dose of [zolpidem](#) SL tablets (Edluar(R)) is 5 or 10 mg SL in men and 5 mg SL in women, given once daily, immediately before bedtime and when at least 7 to 8 hours remain before the planned time of awakening. The dose should be individualized, using the lowest effective dose. Total dose should not exceed 10 mg/day. If insomnia fails to respond to [zolpidem](#) within 7 to 10 days, reevaluate the patient for an underlying primary psychiatric or physical condition [15].

1.3.2] Dosage in [Renal Failure](#)

A) [Zolpidem](#) Tartrate

1) No dosage adjustment is recommended for patients with renal dysfunction. Unchanged drug did not accumulate after 14 or 21 days in patients with [end-stage renal failure](#). Also [zolpidem](#) pharmacokinetics were not significantly different in renally-impaired patients; however, the manufacturer recommends close monitoring [15] [11] [12] [1] [13].

1.3.3] Dosage in Hepatic Insufficiency**A) Zolpidem Tartrate****1) Sublingual Tablets**

a) Edluar(R): Reduce the SL tablet dose to 5 mg once daily immediately before bedtime in patients with [hepatic insufficiency](#) [15].

b) Intermezzo(R): Reduce the SL tablet dose to 1.75 mg orally once at night as needed in patients with [hepatic insufficiency](#) [1].

2) Oral Spray

a) Reduce the oral spray dose to 5 mg once daily immediately before bedtime in patients with [hepatic insufficiency](#) [13].

3) Immediate-Release Tablets

a) Plasma protein binding of [zolpidem](#) is decreased in the presence of [hepatic impairment](#) [30]. The dose of [zolpidem](#) should be reduced to 5 mg in patients with [cirrhosis](#) or other [hepatic impairment](#), due to large increases in half-life, peak plasma concentrations, and AUC [11] [31].

4) Extended-Release Tablets

a) The recommended dose of [zolpidem](#) extended-release tablet is 6.25 mg in patients with [cirrhosis](#) or other [hepatic impairment](#), due to large increases in half-life, peak plasma concentrations, and AUC [12].

1.3.4] Dosage in Geriatric Patients**A) Zolpidem Tartrate****1) SL Tablets**

a) Edluar(R): Reduce the SL tablet dose to 5 mg once daily immediately before bedtime in elderly patients [15].

b) Intermezzo(R): Reduce the SL tablet dose to 1.75 mg orally once at night as needed in patients with [hepatic insufficiency](#) [1].

2) Oral Spray

a) Reduce the oral spray dose to 5 mg once daily immediately before bedtime in elderly patients [13].

3) Immediate-Release Tablets

a) In elderly patients, the dose of [zolpidem](#) should be reduced to 5 mg [11] [31].

1) Any given dose results in 55% higher peak plasma concentrations [32].

4) Extended-Release Tablets

a) The recommended dose of [zolpidem](#) extended-release is 6.25 mg in elderly and/or debilitated patients in order to decrease the potential for side effects. These patients should be closely monitored for impaired motor and/or cognitive performance from repeated exposure to [zolpidem](#) [12].

1.3.5] Dosage Adjustment During Dialysis

A) [Zolpidem](#) Tartrate

1) Hemodialysis

a) [Zolpidem](#) is not dialyzable [15] [11] [12] [1].

b) [Hemodialysis](#) appears to increase [zolpidem](#) protein binding [30]. Dosage adjustment may therefore be necessary under these circumstances, but this has not yet been determined.

c) A slower elimination rate of [zolpidem](#) has been reported in patients undergoing periodic dialysis. Because [zolpidem](#) is not removed in the dialysate, dosage reductions are advised [31].

1.3.6] Dosage in Other Disease States

A) [Zolpidem](#) Tartrate

1) Concomitant Use with CNS Depressants

a) Regardless of gender, the recommended dose of [zolpidem](#) tartrate SL tablets (Intermezzo(R)) in patients taking concomitant CNS depressants is 1.75 mg orally taken once at night as needed. The use of other sedative-hypnotics (including other [zolpidem](#) formulations) at bedtime or in the middle of the night is not recommended [1].

b) Dose reduction may be necessary if [zolpidem](#) tartrate SL tablets (Edluar(R)) are used in combination with other CNS depressants [15].

2) Debilitated Patients

a) In debilitated patients, reduce the dose to 5 mg orally immediately before bedtime for the immediate-release tablets and oral spray, 5 mg SL immediately before bedtime for the SL tablets (Edluar(R)), and 6.25 mg orally immediately before bedtime for the extended-release tablets [15] [11] [12] [13].

1.4] Pediatric Dosage

1.4.1] Normal Dosage

1.4.1.A] Zolpidem Tartrate**1.4.1.A.1] Oral route**

a) The safety and effectiveness of zolpidem in pediatric patients have not been determined [11] [12] [13].

1.4.1.A.2] Sublingual route

a) The safety and effectiveness of zolpidem in pediatric patients have not been determined [15] [1].

2.0] Pharmacokinetics**Drug Concentration Levels****ADME****2.2] Drug Concentration Levels****A) Zolpidem Tartrate****1) Peak Concentration****a) Extended-Release Tablets**

1) Oral, single-dose, healthy male subjects: 134 nanograms/milliliter (12.5 mg) [114]

a) In healthy male subjects, the mean C_{max} was 134 nanograms/milliliter (ng/mL) (range, 68.9 to 197 ng/mL) following a single oral dose of zolpidem extended-release 12.5 mg [114].

2) Oral, female subjects: 50% greater than males [12]

a) Due to decreased clearance in females, the C_{max} was 50% higher in female subjects compared with males when given the same dose of zolpidem extended-release tablets. Blood levels of zolpidem were increased 2- to 3-fold in females compared with males when evaluated between 6 and 12 hours after dosing with the extended-release product [12].

3) Oral, single-dose, elderly subjects: 70.6 nanograms/mL (6.25 mg) [114]

a) In 24 healthy elderly (65 years and older) subjects, the mean C_{max} was 70.6 nanograms/milliliter (ng/mL) (range, 35 to 161 ng/mL) following a single oral dose of zolpidem extended-release 6.25 mg [114].

b) Immediate-Release Tablets

1) Oral, single-dose, healthy male subjects: 59 nanograms/milliliter (ng/mL) (5 mg); 121 ng/mL (10 mg) [33]

a) In a crossover study in 45 healthy male volunteers, the mean C_{max} values were 59 nanograms/milliliter (ng/mL) (range, 29 to 113 ng/mL) and 121 ng/mL (range,

58 to 272 ng/mL) following a single oral dose of zolpidem immediate-release 5 mg and 10 mg, respectively [33].

2) Oral, female subjects: 45% greater than males [11]

a) Due to decreased clearance in females, the C_{max} was 45% higher in female subjects compared with males when given the same dose of zolpidem immediate-release tablets [11].

3) Oral, single-dose, elderly subjects: 384 nanograms/milliliter (20 mg) [33]

a) The mean C_{max} was increased by 50% in 8 healthy elderly subjects 70 years of age and older compared with younger subjects 20 to 40 years of age (384 versus 255 nanograms/milliliter) following a single oral dose of zolpidem immediate-release 20 mg [33].

4) Oral, single-dose, subjects with chronic hepatic insufficiency: 499 nanograms/milliliter (20 mg) [33]

a) The mean C_{max} was 2-fold higher in 8 subjects with chronic hepatic insufficiency compared with healthy subjects (499 versus 250 nanograms/milliliter) following a single oral dose of zolpidem immediate-release 20 mg [33].

5) Oral, multiple-dose, subjects with ESRD on hemodialysis: 203 nanograms/milliliter (10 mg) [33]

a) Following oral administration of zolpidem immediate-release 10 mg/day for 14 to 21 days, the mean C_{max} was 203 +/- 32 nanograms/milliliter (ng/mL) (range, 28 to 316 ng/mL) in 11 subjects with end-stage renal failure (mean CrCl, 6.5 +/- 1.5 mL/min) receiving hemodialysis 3 times/week. After adjusting for baseline concentrations, there was no difference in C_{max} values between day one and the last day of zolpidem administration [33].

c) Sublingual Tablets

1) SL (Intermezzo(R)), healthy male subjects: 53 nanograms/milliliter (3.5 mg) [1]

a) In healthy men (age, 21 to 45 years) who received zolpidem 3.5 mg SL (Intermezzo(R)), the mean C_{max} was 53 nanograms/milliliter [1].

2) SL (Intermezzo(R)), healthy female subjects: 77 nanograms/milliliter (ng/mL) (3.5 mg); 37 ng/mL (1.75 mg) [34]

a) In healthy women (age, 21 to 45 years) who received zolpidem 3.5 mg SL (Intermezzo(R)), the mean C_{max} was 77 nanograms/milliliter (ng/mL). With a dose of 1.75 mg, the mean C_{max} was 37 ng/mL [1].

3j) SL (Intermezzo(R)), elderly subjects: increased by 34% (3.5 mg) [1]

a) In elderly subjects who received zolpidem 3.5 mg SL (Intermezzo(R)), the C_{max} was 34% higher than the C_{max} in non-elderly subjects. With a dose of 1.75 mg, the C_{max} in elderly subjects was lower than the C_{max} with 3.5 mg in non-elderly subjects, but higher than the C_{max} with 1.75 mg in non-elderly subjects [1].

4j) SL (Edluar(R)), single-dose: 106 nanograms/milliliter (10 mg) [34]

a) Zolpidem SL tablets (Edluar(R)) are bioequivalent to zolpidem immediate-release tablets, therefore, the C_{max} levels are similar. In 18 healthy adult subjects (18 to 65 years of age), the mean C_{max} was 106 nanograms/milliliter (ng/mL) (range: 52 to 205 ng/mL) following a single SL dose of zolpidem 10 mg [34].

5j) SL (Edluar(R)), non-elderly female subjects: 45% greater than non-elderly males [15]

a) Due to decreased clearance in non-elderly, adult females, the C_{max} was 45% higher in female subjects compared with non-elderly, adult men when given the same dose of zolpidem tartrate [15].

dj) Oral Spray**1j) Oral, single-dose, healthy subjects: 114 nanograms/milliliter (ng/mL) (5 mg), 210 ng/mL (10 mg) [13]**

a) The mean C_{max} was 114 nanograms/milliliter (ng/mL) (range, 19 to 197 ng/mL) and 210 ng/mL (range, 77 to 401 ng/mL) for 5 mg and 10 mg, respectively, of oral spray zolpidem in a single-dose crossover study in 43 healthy subjects (18 to 45 years of age) [13].

2j) Oral, single-dose, elderly subjects: 134 nanograms/milliliter (5 mg) [13]

a) In 24 elderly (65 years and older) subjects, the C_{max} was 134 nanograms/milliliter following a single 5 mg oral spray of zolpidem [13].

2j) Time to Peak Concentration**a) Extended-Release Tablets****1j) Oral, healthy male subjects: 1.5 hours (12.5 mg) [114]**

a) In healthy male subjects, the mean C_{max} of 134 nanograms/milliliter (ng/mL) (range: 68.8 to 197 ng/mL) occurred at a median T_{max} of 1.5 hours following a single oral dose of zolpidem extended-release 12.5 mg [114].

2j) Oral, elderly subjects: 2 hours (6.25 mg) [114]

a) In 24 healthy elderly (65 years and older) subjects, the mean C_{max} of 70.6 nanograms/milliliter (ng/mL) (range, 35 to 161 ng/mL) occurred at a median T_{max} of 2 hours following a single oral dose of zolpidem extended-release 6.25 mg [114].

b)) Immediate-Release Tablets

1)) Oral, healthy male subjects: 1.6 hours (5 mg and 10 mg) [33]

a) In a crossover study in 45 healthy male volunteers, the mean C_{max} values of 59 nanograms/milliliter (ng/mL) (range, 29 to 113 ng/mL) and 121 ng/mL (range, 58 to 272 ng/mL) occurred at a mean T_{max} of 1.6 hours following a single oral dose of zolpidem immediate-release 5 mg and 10 mg, respectively [33].

2)) Oral, elderly subjects: 2.9 hours (20 mg) [33]

a) The mean T_{max} was increased by 32% in 8 healthy elderly subjects 70 years of age and older compared with younger subjects 20 to 40 years of age (2.9 versus 2.2 hours) following a single oral dose of zolpidem immediate-release 20 mg [33].

3)) Oral, ESRD on hemodialysis: 0.8 hours (10 mg) [33]

a) Following oral administration of zolpidem immediate-release 10 mg/day for 14 to 21 days, the mean C_{max} of 203 +/- 32 nanograms/milliliter (ng/mL) (range, 28 to 316 ng/mL) occurred at a mean T_{max} of 0.8 +/- 0.2 hours (range, 0.5 to 2 hours) in 11 subjects with end-stage renal failure (mean CrCl, 6.5 +/- 1.5 mL/min) receiving hemodialysis 3 times/week. After adjusting for baseline concentrations, there was no difference in T_{max} values between day one and the last day of zolpidem administration [33].

c)) Sublingual Tablets

1)) SL (Intermezzo(R)): 35 to 75 minutes [1]

a) Mean T_{max} across studies was approximately 35 to 75 minutes [1].

2)) SL (Edluar(R)): 82 minutes (10 mg) [34]

a) In 18 healthy adult subjects (18 to 65 years of age), the mean C_{max} of 106 nanograms/milliliter (ng/mL) (range: 52 to 205 ng/mL) occurred at a median T_{max} of 82 minutes (range, 30 to 180 minutes) following a single SL dose of zolpidem 10 mg [34].

d)) Oral Spray

1)) Oral: 0.9 hours [13]

a) The mean time to reach a C_{max} of 114 nanograms/milliliter (ng/mL) (range, 19 to 197 ng/mL) and 210 ng/mL (range, 77 to 401) was 0.9 hours for both 5 mg and 10 mg of oral spray zolpidem in a single-dose crossover study in 43 healthy subjects (18 to 45 years of age) [13].

3) Area Under the Curve

a) Extended-Release Tablets

1) Oral, single-dose, healthy male subjects: 740 nanograms x hr/mL (12.5 mg) [114]

a) In healthy male subjects, the mean AUC was 740 nanograms x hr/mL (range, 295 to 1359 nanograms x hr/mL) following a single oral dose of zolpidem extended-release 12.5 mg [114].

2) Oral, female subjects: 75% greater than males [12]

a) Due to decreased clearance in females, the AUC was 75% higher in female subjects compared with males when given the same dose of zolpidem tartrate extended-release tablet [12].

3) Oral, single-dose, elderly subjects: 413 nanograms x hr/mL (6.25 mg) [114]

a) In 24 healthy elderly (65 years and older) subjects, the AUC was 413 nanograms x hr/mL (range, 124 to 1190 nanograms x hr/mL) following a single oral dose of zolpidem extended-release 6.25 mg [114].

b) Immediate-Release Tablets

1) Oral, single-dose, healthy male subjects: 408 nanograms x hr/mL (10 mg); 889 nanograms x hr/mL (20 mg) [118]

a) In a double-blind crossover study in 10 healthy male volunteers, the mean AUC values were 408 nanograms x hr/mL and 889 nanograms x hr/mL following a single oral dose of zolpidem immediate-release 10 mg and 20 mg, respectively [118].

2) Oral, female subjects: 45% greater than males [11]

a) Due to decreased clearance in females, the AUC was 45% higher in female subjects compared with males when given the same dose of zolpidem immediate-release tablets [11].

3) Oral, single-dose, elderly subjects: 1562 nanograms x hr/mL (20 mg) [33]

a) The mean AUC was increased by 64% in 8 healthy elderly subjects 70 years of age and older compared with younger subjects 20 to 40 years of age (1562 versus

955 nanograms x hr/mL) following a single oral dose of zolpidem immediate-release 20 mg [33].

4) Oral, single-dose, subjects with chronic hepatic insufficiency: 4203 nanograms x hr/mL (20 mg) [33]

a) The mean AUC was 5-fold higher in 8 subjects with chronic hepatic insufficiency compared with healthy subjects (4203 versus 788 nanograms x hr/mL) following a single oral dose of zolpidem immediate-release 20 mg [33].

5) Oral, multiple-dose, subjects with ESRD on hemodialysis: 818 nanograms x hr/mL (10 mg) [33]

a) Following oral administration of zolpidem immediate-release 10 mg/day for 14 to 21 days, the mean AUC was 818 +/- 170 nanograms x hr/mL in 11 subjects with end-stage renal failure (mean CrCl, 6.5 +/- 1.5 mL/min) receiving hemodialysis 3 times/week. After adjusting for baseline concentrations, there was no difference in AUC values between day one and the last day of zolpidem administration [33].

c) Sublingual Tablets

1) SL (Intermezzo(R)), healthy male subjects: 198 nanograms x hr/mL (3.5 mg) [1]

a) In healthy men (age, 21 to 45 years) who received zolpidem 3.5 mg SL (Intermezzo(R)), the mean AUC was 198 nanograms x hr/mL [1].

2) SL (Intermezzo(R)), healthy female subjects: 296 nanograms x hr/mL (3.5 mg); 151 nanograms x hr/mL (1.75 mg) [34]

a) In healthy women (age, 21 to 45 years) who received zolpidem SL 3.5 mg (Intermezzo(R)), the mean AUC was 296 nanograms x hr/mL. With a dose of 1.75 mg, the mean AUC was 151 nanograms x hr/mL [1].

3) SL (Intermezzo(R)), elderly subjects: increased by 30% (3.5 mg) [1]

a) In elderly subjects who received zolpidem 3.5 mg SL (Intermezzo(R)), the AUC(0 to 4 hours) was 30% higher than the AUC in non-elderly subjects. With a dose of 1.75 mg, the AUC in elderly subjects was lower than the AUC with 3.5 mg in non-elderly subjects, but higher than the AUC with 1.75 mg in non-elderly subjects [1].

4) SL (Edluar(R)), single-dose: bioequivalent to zolpidem immediate-release tablets [34]

a) Zolpidem SL (Edluar(R)) are bioequivalent to zolpidem immediate-release tablets; therefore, the AUC values are similar [34].

5) SL (Edluar(R)), non-elderly female subjects: 45% greater than non-elderly males [15]

a) Due to decreased clearance in adult females, the AUC was 45% higher in female subjects compared with adult men when given the same dose of zolpidem tartrate [15].

d) Oral Spray

1) Oral, single-dose: bioequivalent to zolpidem immediate-release tablets [13]

a) Zolpidem oral spray is bioequivalent to zolpidem immediate-release tablets; therefore, the AUC values are similar [13]

2) Oral, single-dose, elderly patients: 493 nanograms x hr/mL (5 mg) [13]

a) In 24 elderly (65 years and older) subjects, the AUC was 493 nanograms x hr/mL following a single 5 mg oral spray of zolpidem [13].

2.3] ADME

2.3.1] Absorption

A) Zolpidem Tartrate

1) Bioavailability

a) Oral, tablets: 70% [119] [120].

1) Zolpidem bioavailability is about 70% due to substantial first-pass metabolism [120].

2) Effects of Food

a) Tablets

1) decreased systemic exposure [114] [33] [34].

a) For faster sleep onset, zolpidem should not be administered with or immediately after food [114] [33] [34].

b) In a food effect study in 45 healthy subjects, the mean C_{max} was decreased by 30% and mean AUC was decreased by 23% following a single oral dose of zolpidem extended-release 12.5 mg administered 30 minutes after a meal compared to zolpidem administered under fasting conditions. Additionally, the T_{max} was increased from 2 to 4 hours when zolpidem extended-release 12.5 mg was administered 30 minutes after a meal [114].

c) In a food effect study in 30 healthy subjects, the mean C_{max} was decreased by 25%, the mean AUC was decreased by 15%, and the mean T_{max} was

increased by 60% (from 1.4 to 2.2 hours) following a single oral dose of zolpidem immediate-release 10 mg administered 20 minutes after a meal compared to zolpidem administered under fasting conditions . [33].

d) In a food effect study in 18 healthy subjects, the mean C_{max} was decreased by 31%, the mean AUC was decreased by 20%, and the mean T_{max} was increased by 28% (from 82 to 105 minutes) following a single SL dose of zolpidem 10 mg administered 20 minutes after a high-fat meal compared to zolpidem administered under fasting conditions [34].

b) Sublingual Tablets

1) (Intermezzo(R)), decreased systemic exposure [1]

a) After administration of SL zolpidem (Intermezzo(R)) with food, C_{max} was reduced by 42%, AUC was reduced by 19%, and T_{max} was increased to nearly 3 hours [1].

c) Oral Spray

1) decreased systemic exposure [13]

a) Mean AUC and C_{max} decreased by 27% and 58%, respectively, and mean T_{max} was delayed by 225% (from 0.8 to 2.6 hours) when oral spray zolpidem 10 mg was administered with a high-fat meal in a crossover study of 14 healthy male subjects (18 to 45 years of age). Zolpidem oral spray should not be administered with or immediately after a meal [13].

2.3.2] Distribution

A) Distribution Sites

1) Zolpidem Tartrate

a) Protein Binding

1) 92.5% [1] [114] [33] [34] [13]

a) Protein binding is not concentration-dependent and remains constant at 92.5% +/- 0.1% between concentrations of 40 to 790 nanograms/milliliter of zolpidem based on data from orally administered zolpidem [1] [114] [33] [34] [13].

b) Zolpidem protein binding is markedly reduced in the presence of hepatic or renal impairment. The unbound fraction of zolpidem was about 8% in 6 normal individuals, but in 12 patients with cirrhosis, the unbound fraction was approximately 11.3%. In 12 patients with renal failure, the unbound

fraction was approximately 10.8%. However, the clinical significance of this is unknown [121].

c) Hemodialysis appears to increase zolpidem protein binding. A mean unbound fraction of 14.9% was reported in 12 chronic uremic patients before undergoing hemodialysis, and an unbound fraction of 9.8% after dialysis [121].

B) Distribution Kinetics

1) Zolpidem Tartrate

a) Volume of Distribution

1) 0.54 L/kg [120]

2.3.3] Metabolism

A) Metabolism Sites and Kinetics

1) Zolpidem Tartrate

a) Liver, extensive [120]

1) Zolpidem is hepatically metabolized via oxidation of the methyl group to produce carboxylic acids, hydroxylation of the imidazopyridine group and oxidation of the methyl groups on the substituted amide [119] [120].

2.3.4] Excretion

A) Kidney

1) Zolpidem Tartrate

a) Renal Excretion (%)

1) less than 1% [120]

a) Zolpidem is metabolized to inactive metabolites which are mostly excreted renally [1] [114] [33] [34] [13].

B) Total Body Clearance

1) Zolpidem Tartrate

a) 0.26 L/hr/kg [120]

b) Female subjects: reduced [15] [11] [12]

1j) Clearance of zolpidem is reduced in adult female subjects compared with adult males when given the same dose of zolpidem extended-release, immediate-release, or SL (Edluar(R)) tablets. This results in increased blood levels, C_{max}, and AUC of zolpidem in adult females. Elderly females had clearance similar to elderly males [15] [11] [12].

2.3.5] Elimination Half-life

Aj) Parent Compound

1j) Zolpidem Tartrate

aj) Extended-Release Tablets

1j) 2.8 hours, healthy male subjects; 2.9 hours, elderly subjects [114]

a) In healthy male subjects, the mean elimination half-life was 2.8 hours (range, 1.62 to 4.05 hours) following a single oral dose of zolpidem extended-release 12.5 mg [114].

b) In 24 healthy elderly (65 years and older) subjects, the mean elimination half-life was 2.9 hours (range, 1.59 to 5.5 hours) following a single oral dose of zolpidem extended-release 6.25 mg [114].

bj) Immediate-Release Tablets

1j) 2.5 to 2.6 hours, healthy male subjects; 2.9 hours, elderly subjects; 9.9 hours, cirrhotic patients; 2.5 hours, end-stage renal failure patients on hemodialysis [33]

a) In a crossover study in 45 healthy male volunteers, the mean elimination half-life values were 2.6 hours (range, 1.4 to 4.5 hours) and 2.5 hours (range, 1.4 to 3.8 hours) following a single oral dose of zolpidem immediate-release 5 mg and 10 mg, respectively [33].

b) The mean elimination half-life was increased by 32% in 8 healthy elderly subjects 70 years of age and older compared with younger subjects 20 to 40 years of age (2.9 versus 2.2 hours) following a single oral dose of zolpidem immediate-release 20 mg [33].

c) The mean elimination half-life was 9.9 hours (range, 4.1 to 25.8 hours) in cirrhotic patients compared with 2.2 hours (range, 1.6 to 2.4 hours) in healthy subjects following a single oral dose of zolpidem immediate-release 20 mg [33].

d) Following oral administration of zolpidem immediate-release 10 mg/day for 14 to 21 days, the mean elimination half-life was 2.5 +/- 0.4 hours (range, 0.7 to 4.2 hours) in 11 subjects with end-stage renal failure (mean CrCl, 6.5 +/- 1.5 mL/min) receiving hemodialysis 3 times/week. After adjusting for baseline

concentrations, there was no difference in elimination half-life values between day one and the last day of zolpidem administration [33].

c) Sublingual Tablets

1) 2.5 hours (Intermezzo(R)) [1]

a) After administration of a single dose of zolpidem 3.5 mg SL (Intermezzo(R)), the elimination $t(1/2)$ was approximately 2.5 hours (range, 1.4 to 3.6 hours). Elimination $t(1/2)$ was not different in elderly subjects compared with non-elderly subjects [1].

2) 2.65 to 2.85 hours (Edluar(R)) [34]

a) In healthy adult subjects, the mean elimination half-life values were 2.85 hours (range, 1.57 to 6.73 hours) and 2.65 hours (range, 1.75 to 3.77 hours) following a single SL dose of zolpidem 5 mg and 10 mg, respectively [34].

d) Oral Spray

1) 2.7 to 3 hours [13]

a) The mean half-life was 2.7 hours (range, 1.7 to 5 hours) and 3 hours (range, 1.7 to 8.4 hours) for 5 mg and 10 mg, respectively, of oral spray zolpidem in a single-dose crossover study in 43 healthy subjects (18 to 45 years of age) [13].

2.3.6] Extracorporeal Elimination

A) Hemodialysis

1) Zolpidem Tartrate

a) Dialyzable: No [33]

1) Zolpidem tartrate is not removed by hemodialysis [33].

3.0] Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.1] Contraindications

A) Zolpidem Tartrate

1)) hypersensitivity to [zolpidem](#) tartrate [15] [12] [11] [1] [13]

3.2] Precautions

A) [Zolpidem](#) Tartrate

1)) abrupt withdrawal or rapid dose decrease may cause severe withdrawal symptoms [12] [11] [1] [13]

2)) [anaphylaxis](#) may occur with first or subsequent doses [15] [12] [11] [1] [13]

3)) [angioedema](#), involving the tongue, glottis, or larynx, may occur with first or subsequent doses [15] [12] [11] [1] [13]; do not rechallenge if [angioedema](#) occurs [15] [12] [11]

4)) behavioral changes and abnormal thinking (eg, hallucinations, bizarre behavior, agitation, and depersonalization) have been reported [15] [12] [11] [1] [13]

5)) CNS depression has been reported; increased risk with concomitant use of other CNS depressants (eg, benzodiazepines, opioids, tricyclic antidepressants); dose adjustments may be required [15] [12] [11]

6)) concomitant use with other sedative-hypnotics (including other [zolpidem](#) products) at bedtime or the middle of the night is not recommended [15] [12] [11] [1]

7)) concurrent use of alcohol should be avoided [15] [12] [11] [13]

8)) depression; may exacerbate symptoms, including suicidal thinking [15] [12] [11] [1] [13]

9)) diseases or conditions that affect metabolism or hemodynamic response (oral spray) [13]

10)) driving or [psychomotor impairment](#), next-day; increased risk if dose is taken with less than 4 hours (Intermezzo(R)) [1] or 7 to 8 hours (Edluar(R), [Ambien](#)(R) or [Ambien CR](#)(R)) [15] [12] [11] of sleep remaining, if exceeding recommended dose, with concurrent use of other CNS depressants, or with concurrent use of other drugs that increase the blood levels of [zolpidem](#) [15] [12] [11] [1]

11)) elderly [15] [11] [12] [1] [13] or debilitated patients [15] [11] [12] [13]; increased risk of impaired motor and/or cognitive performance; dose reduction recommended [15] [12] [11] [1] [13]

12)) female patients; reduced drug clearance has been observed compared with male patients [15] [11] [12]

13)) [hepatic impairment](#); dose reduction recommended [15] [11] [12] [1] [13]

14)) [renal impairment](#) (oral spray) [13]

15)) respiratory impairment; may depress respiratory drive; increased risk in patients with [sleep apnea](#) or [myasthenia gravis](#) [15] [12] [11] [1] [13]

16)) sleep-related behaviors, complex, have been reported; possibility of patients performing activities while asleep (eg, sleep-driving, making phone calls, preparing/eating food, having sex) with no memory afterwards; increased risk with doses higher than recommended and concomitant use of CNS depressants and alcohol; discontinuation may be necessary if sleep-driving occurs [15] [12] [11] [1] [13]

17)) underlying comorbid physical or psychiatric disorders; worsening of insomnia, failure of insomnia to remit after 7 to 10 days, or emergence of new behavioral or cognitive abnormalities may indicate the presence of a primary medical and/or psychiatric illness [15] [12] [11] [1] [13]

18)) report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or www.fda.gov/medwatch [15] [12] [11] [1] [13]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Zolpidem Tartrate

3.3.1.A.1] Chest pain

a) Incidence: 1% [33] [34] [13]

b) Chest pain was reported in 1% of **chronic insomnia** patients receiving immediate-release **zolpidem** tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.1.A.2] Hypertension

a) Incidence: 0.1% to 1% [33] [34] [13]

b) **Hypertension** was reported in 0.1% to 1% of 3660 patients receiving **zolpidem** tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.1.A.3] Palpitations

a) Incidence: 2% [33] [34] [13]

b) Palpitations were reported in 2% of **chronic insomnia** patients receiving immediate-release **zolpidem** tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.1.A.4] Tachycardia

a) Incidence: 0.1% to 1% [33] [34] [13]

b) **Tachycardia** was reported in 0.1% to 1% of 3660 patients receiving **zolpidem** tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.2] Dermatologic Effects

3.3.2.A] Zolpidem Tartrate

3.3.2.A.1] Rash

a) Incidence: 2% [33] [34] [13]

b) Rash was reported in 2% of **chronic insomnia** patients receiving immediate-release **zolpidem** tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.4] Gastrointestinal Effects

3.3.4.A] Zolpidem Tartrate

3.3.4.A.1] Constipation

- a) Incidence: 2% [33] [34] [13]
- b) Constipation was reported in 2% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.4.A.2] Diarrhea

- a) Incidence: 1% to 3% [33] [34] [13]
- b) Diarrhea was reported in 3% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 2% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].
- c) During short-term trials (up to 10 nights), diarrhea was reported in 1% of patients receiving immediate-release [zolpidem](#) tartrate 10 mg or less per night (n=685) compared with 0% of patients receiving placebo (n=473) [33] [34] [13].

3.3.4.A.3] Erythema of mucous membrane of mouth

- a) Transient sublingual erythema occurred in one patient after chronic daily use of [zolpidem](#) tartrate sublingual tablets for insomnia in a 60-day, open-label trial (n=60) [34].

3.3.4.A.4] Indigestion

- a) Incidence: 1% or greater [33] [34] [13]
- b) [Dyspepsia](#) was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.4.A.5] Nausea

- a) Incidence: 1% to 7% [1] [33] [34] [13] [38]
- b) Nausea was reported in 1% of patients who took [zolpidem](#) sublingual tablets 3.5 mg (Intermezzo(R); n=150) and 1% of patients who took placebo (n=145) on an as needed basis for middle-of-the-night awakenings, in a 4-week, double-blind, placebo-controlled, outpatient study of adult patients with insomnia. [Zolpidem](#) sublingual tablets were taken on 62% of the study nights. Adverse reaction incidence rates were similar in patients receiving [zolpidem](#) 1.75 mg during a double-blind, placebo-controlled, 3-period crossover sleep laboratory study (n=82) [1].
- c) Nausea was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].
- d) During a three-week clinical trial, nausea was reported in 7% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); this adverse effect occurred in 4% of patients in the placebo group (n=110) [38].

3.3.4.A.6] Paresthesia, tongue

- a) Transient paresthesia of the tongue occurred in one patient after chronic daily use of [zolpidem](#) tartrate sublingual tablets for insomnia in a 60-day, open-label trial (n=60) [34].

3.3.4.A.7] Xerostomia

- a) Incidence: 3% [33] [34] [13]

b) Dry mouth was reported in 3% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.6] Hepatic Effects

3.3.6.A] [Zolpidem Tartrate](#)

3.3.6.A.1] [Abnormal liver function](#)

a) Incidence: 0.1% to 1% [33] [34] [13]

b) [Abnormal hepatic function](#) was reported in 0.1% to 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.6.A.2] [ALT/SGPT level raised](#)

a) Incidence: 0.1% to 1% [33] [34] [13]

b) Increased SGPT was reported in 0.1% to 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.6.A.3] [Hepatotoxicity](#)

a) A 53-year-old woman suffered [acute hepatitis](#) mimicking biliary [lithiasis](#) after taking [zolpidem](#) 20 mg. [Zolpidem](#) was not clearly linked to this episode and consequently the woman again ingested the drug. This time she developed sudden epigastric pain and [jaundice](#). Her liver function tests were elevated with [alanine aminotransferase](#) at 596 international units/L, [aspartate aminotransferase](#) at 198 international units/L, gamma-glutamyl transpeptidase at 242 international units/L, and [alkaline phosphatase](#) at 134 international units/L. She received the drug a third time and liver enzymes were again elevated. Liver enzymes returned to normal after cessation of [zolpidem](#) therapy [40].

3.3.7] Immunologic Effects

3.3.7.A] [Zolpidem Tartrate](#)

3.3.7.A.1] [Allergy](#)

a) Incidence: 4% [33] [34] [13]

b) Allergy was reported in 4% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.7.A.2] [Anaphylaxis](#)

a) Incidence: rare [33] [34] [13] [38]

b) Cases of [angioedema](#) involving the tongue, glottis, or larynx, some fatal, have been reported rarely in patients following the first or subsequent dose of sedative-hypnotics, including [zolpidem](#). Additional symptoms suggestive of [anaphylaxis](#), including dyspnea, throat closing, or nausea and vomiting, have been reported. Some patients with these symptoms have presented to the emergency department. Do not rechallenge patients who have experienced [angioedema](#) following [zolpidem](#) treatment [1] [33] [34] [13] [38].

3.3.8] Musculoskeletal Effects

3.3.8.A] Zolpidem Tartrate

3.3.8.A.1] Arthralgia

- a) Incidence: 1% or greater [33] [34] [13]
- b) Arthralgia was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.8.A.2] Backache

- a) Incidence: 3% [33] [34] [13]
- b) Back pain was reported in 3% of chronic insomnia patients receiving immediate-release zolpidem tartrate 5 mg or 10 mg per night (n=152) compared with 2% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.8.A.3] Myalgia

- a) Incidence: 1% to 4% [33] [34] [13] [38]
- b) Myalgia was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].
- c) During a three-week clinical trial, myalgia occurred in 4% of patients who received extended-release zolpidem 12.5 mg (n=102); the incidence was 0% in the placebo group (n=110) [38].

3.3.9] Neurologic Effects

3.3.9.A] Zolpidem Tartrate

3.3.9.A.1] Asthenia

- a) Incidence: 1% or greater [33] [34] [13]
- b) Asthenia was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.9.A.2] Ataxia

- a) Incidence: 1% or greater [33] [34] [13] [38]
- b) Ataxia was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].
- c) During a three-week clinical trial, ataxia occurred in 1% of patients who received extended-release zolpidem 12.5 mg (n=102); this adverse effect occurred in 0% of patients in the placebo group (n=110) [38].
- d) Confusion and falls have been reported with normal therapeutic doses of zolpidem in elderly patients; the incidence of each was related to patient age and the dosage used. Memory disturbance has also been reported without an apparent relationship to age, sex, or treatment duration [31].

3.3.9.A.3] Cerebrovascular disease

a) Incidence: 0.1% to 1% [33] [34] [13]

b) **Cerebrovascular disorder** was reported in 0.1% to 1% of 3660 patients receiving **zolpidem** tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.9.A.4] Confusion

a) Incidence: 1% or greater [33] [34] [13]

b) Confusion was reported in at least 1% of 3660 patients receiving **zolpidem** tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

c) Confusion and falls have been reported with normal therapeutic doses of **zolpidem** in elderly patients; the incidence of each was related to patient age and the dosage used. **Memory disturbance** has also been reported without an apparent relationship to age, sex or treatment duration [31].

3.3.9.A.5] Difficulty driving a car

a) Driving was significantly impaired 3 hours after taking **zolpidem** sublingual tablets 3.5 mg (Intermezzo(R)) and was impaired 4 hours after taking **zolpidem** (though not a statistically significant difference from placebo) in healthy subjects in a randomized, double-blind, single-center, 4-period, crossover study (n=40). Randomized treatments included (1) **zolpidem** sublingual tablets 3.5 mg (Intermezzo(R)) 4 hours before driving, (2) **zolpidem** sublingual tablets 3.5 mg (Intermezzo(R)) 3 hours before driving, (3) placebo, and (4) positive control (unapproved sedative-hypnotic) 9 hours before driving. Driving impairment was measured by the change in standard deviation of lateral position (SDLP; primary outcome) using a symmetry analysis to determine the proportion of subjects whose change from their placebo SDLP was statistically significantly above a threshold for clinically meaningful driving impairment. There was a statistically significant impairing effect at 3 hours, and a numerical, but not statistically significant, difference from placebo at 4 hours. The risk of next-day driving impairment and **psychomotor impairment** is increased if administration occurs with less than 4 hours of bedtime remaining, if a higher than recommended dose is used, or if coadministered with other CNS depressants or drugs that increase the plasma concentration of **zolpidem** [1].

3.3.9.A.6] Disorientated

a) Incidence: 3% [38]

b) During a three-week clinical trial, disorientation occurred in 3% of patients who received extended-release **zolpidem** 12.5 mg (n=102); this adverse effect occurred in 2% of patients in the placebo group (n=110) [38].

3.3.9.A.7] Dizziness

a) Incidence: 1% to 23.5% [33] [34] [13] [38]

b) During short-term trials (up to 10 nights), dizziness was reported in 1% of patients receiving immediate-release **zolpidem** tartrate 10 mg or less per night (n=685) compared with 0% of patients receiving placebo (n=473) [33] [34] [13].

c) Dizziness was reported in 5% of **chronic insomnia** patients receiving immediate-release **zolpidem** tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights), and was one of the most commonly-reported adverse events during these trials [33] [34] [13].

d) During a three-week clinical trial, dizziness was reported in 12% of patients who received extended-release **zolpidem** 12.5 mg (n=102); this adverse effect occurred in 5% of patients in the placebo group

(n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) tartrate extended-release 6.25 mg (n=99) or placebo (n=106), dizziness was reported in 8% compared to 3% in the placebo group [38].

e) In an 8-week controlled study involving 201 pediatric patients (aged 6 to 17 years) with insomnia associated with ADHD, 23.5% of patients receiving [zolpidem](#) oral solution (n=136) compared with 1.5% of patients receiving placebo (n=65) experienced dizziness [34] [33] [13] [38].

3.3.9.A.8] Drugged state

a) Incidence: 3% [33] [34] [13]

b) Drugged feeling was reported in 3% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights), and was one of the most commonly-reported adverse events during these trials [33] [34] [13].

3.3.9.A.9] Headache

a) Incidence: 1% to 19% [1] [34] [33] [13] [38]

b) Headache was reported in 3% of patients who took [zolpidem](#) sublingual tablets 3.5 mg (Intermezzo(R); n=150) and 1% of patients who took placebo (n=145) on an as needed basis for middle-of-the-night awakenings, in a 4-week, double-blind, placebo-controlled, outpatient study of adult patients with insomnia. [Zolpidem](#) sublingual tablets were taken on 62% of the study nights. Adverse reaction incidence rates were similar in patients receiving [zolpidem](#) 1.75 mg during a double-blind, placebo-controlled, 3-period crossover sleep laboratory study (n=82) [1].

c) During short-term trials (up to 10 nights), headache was reported in 7% of patients receiving immediate-release [zolpidem](#) tartrate 10 mg or less per night (n=685) compared with 6% of patients receiving placebo (n=473) [33] [34] [13].

d) Headache was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

e) During a three-week clinical trial, headache occurred in 19% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); this adverse effect occurred in 16% of patients in the placebo group (n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) tartrate extended-release 6.25 mg (n=99) or placebo (n=106), headache was reported in 14% compared to 11% in the placebo group [38].

f) In an 8-week controlled study involving 201 pediatric patients (aged 6 to 17 years) with insomnia associated with ADHD, 12.5% of patients receiving [zolpidem](#) oral solution (n=136) compared with 9.2% of patients receiving placebo (n=65) experienced headache [34] [33] [13] [38].

3.3.9.A.10] Hepatic encephalopathy

a) A 73-year-old woman with [cryptogenic cirrhosis](#) developed clinical signs of [hepatic encephalopathy](#) after receiving 10 mg of [zolpidem](#) only 12 hours prior before admission to the intensive care unit (ICU). The patient's medical history included [Lewy body dementia](#), transient insomnia, [arterial hypertension](#) and 1 week of [jaundice](#) and ascites. Current medications included [quetiapine](#) 12 mg/day and [rivastigmine](#) 12 mg/day for six months. Upon physical exam, the patient had involuntary movements of the upper limbs, temporal and spatial disorientation, [jaundice](#) and moderate abdominal and ankle swelling. Laboratory analysis revealed elevated liver enzymes (eg, AST (53 international units/L), [ALT](#) (65 international units/L), [alkaline phosphatase](#) (187 international units/L), [gamma-glutamyl transferase](#) (117 international units/L), [bilirubin](#) (3.48 mg/dL)), normal albumin (1.3 grams/dL), and slightly elevated INR (1.75). Immunology screening yielded negative

results and other causes of [chronic liver disease](#) (eg, [hemochromatosis](#), [alcoholic liver disease](#), and [alpha-1-antitrypsin deficiency](#)) were ruled out. Upon ultrasound examination, the liver was shrunken with irregular surface, no biliary dilatation and 3-cm hypoechoic nodule in the left lobe. The alpha-fetoprotein level was 440 international units/L and the [esophagogastroduodenoscopy](#) revealed a small [esophageal varices](#) and moderate hypertensive [gastropathy](#). The patient was diagnosed with [cryptogenic cirrhosis](#) complicated by [hepatocellular carcinoma](#) and ascites and treatment with diuretics (spiro lactone 100 mg/day and [furosemide](#) 40 mg/day) was started. Eight days after admission, the patient developed clinical and laboratory signs of sepsis and acute deterioration of consciousness characterized by torpor that evolved to a Glasgow coma scale of 5. The patient was transferred to the ICU and given a [intravenous injection](#) of [flumazenil](#) 1 mg because the patient had received [zolpidem](#) 10 mg only 12 hours prior. Within 30 seconds after the bolus injection, the patient recovered to her basal state of consciousness. After 14 days, the patient was discharged from the hospital. The half-life of [zolpidem](#) is significantly altered in elderly patients and patients with [chronic liver disease](#) due to hepatic metabolism. The prompt recovery after the use of [flumazenil](#) suggests that [zolpidem](#) may have precipitated the [hepatic encephalopathy](#) [39].

3.3.9.A.11] Lethargy

a) Incidence: 3% [33] [34] [13]

b) Lethargy was reported in 3% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.9.A.12] Lightheadedness

a) Incidence: 2% [34] [33] [13]

b) Lightheadedness was reported in 2% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.9.A.13] Motor retardation

a) Incidence: 2% [38]

b) During a three-week clinical trial, psychomotor retardation was reported in 2% of patients who received either extended-release [zolpidem](#) 12.5 mg or 6.25 mg (n=201); this adverse effect occurred in 0% of patients in the placebo group (n=216) [38].

3.3.9.A.14] Nocturnal sleep-related eating disorder

a) In a case series, the onset or worsening of amnesic nocturnal eating behavior was noted in 5 patients treated with [zolpidem](#) in daily doses of 5 to 30 mg for treatment of sleep-onset insomnia. In 3 of the patients, the nocturnal eating occurred after the [zolpidem](#) therapy was initiated; in the remaining 2 patients the existing nocturnal eating episodes increased in frequency. In all cases, after [zolpidem](#), the patients were amnesic to the nocturnal eating episodes. After discontinuation of [zolpidem](#), the nocturnal eating behavior subsided [35].

b) A case report described [nocturnal sleep-related eating disorder](#) (NSRED) in a 45-year-old man following [zolpidem](#) use for short-term treatment of insomnia. The patient, who was obese (100 kg; BMI 35.85), had no history of recent weight gain or [somnambulism](#) and was not receiving any concomitant medication. Two hours after his tenth bedtime dose of [zolpidem](#) tartrate 10 mg/day, he was found at his place of business 2 km away from home eating sweets. When the patient was awakened, he had no memory of his NSRED episode. Because [zolpidem](#) causality was not suspected,

the patient was continued on his treatment. However, he experienced a similar incident 4 days later at which time [zolpidem](#) was discontinued with no further episodes. According to the Naranjo algorithm, it was highly probable that NSRED was caused by [zolpidem](#) (score of 9) [36].

c) A 46-year-old man experienced [somnia](#) 4 nights after beginning [zolpidem](#) 10 mg nightly. For several nights, his sleepwalking included preparing a meal, consuming it, and returning to bed. His sleepwalking ended with the discontinuation of [zolpidem](#) [37].

3.3.9.A.15] Sleep disorder

a) Incidence: 1% [33] [34] [13]

b) Sleep disorder was reported in 1% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.9.A.16] Somnolence

a) Incidence: 2% to 15% [33] [34] [13] [38]

b) During short-term trials (up to 10 nights), drowsiness was reported in 2% of patients receiving immediate-release [zolpidem](#) tartrate 10 mg or less per night (n=685) compared with 0% of patients receiving placebo (n=473) [33] [34] [13].

c) Drowsiness was reported in 8% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 5% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

d) During a three-week clinical trial, somnolence was reported in 15% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); this adverse effect occurred in 2% of patients in the placebo group (n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) tartrate extended-release 6.25 mg (n=99) or placebo (n=106), somnolence was reported in 6% compared to 5% in the placebo group [38].

3.3.9.A.17] Vertigo

a) Incidence: 1% or greater [33] [34] [13]

b) Vertigo was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.10] Ophthalmic Effects

3.3.10.A] [Zolpidem](#) Tartrate

3.3.10.A.1] Abnormal vision

a) Incidence: 1% or greater [33] [34] [13]

b) Abnormal vision was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.10.A.2] [Diplopia](#)

a) Incidence: 1% or greater [33] [34] [13]

b) [Diplopia](#) was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.10.A.3] Visual disturbance

a)] Incidence: 3% [38]

b)] During a three-week clinical trial, visual disturbances were reported in 3% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); there was no incidence of this adverse effect in the placebo group (n=110) [38].

3.3.12] Psychiatric Effects

3.3.12.A] [Zolpidem](#) Tartrate

3.3.12.A.1] Abnormal behavior

a)] Abnormal thinking and changes in behavior have been reported with the use of sedative/hypnotics. These changes, similar to effects produced by alcohol and other CNS depressants, may include decreased inhibition (eg, aggressiveness and extroversion that seem out of character). Other behavior changes reported include bizarre behavior, agitation, and depersonalization [1] [33] [34] [13].

3.3.12.A.2] Anxiety

a)] Incidence: 2% to 6.3% [38]

b)] During a three-week clinical trial, anxiety was reported in 2% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); this adverse effect occurred in 0% of patients in the placebo group (n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) extended-release 6.25 mg (n=99) or placebo (n=106), anxiety was reported in 3% compared to 2% in the placebo group [38].

c)] In a 6-month trial among 1018 adult patients aged 18 and 64 years, [zolpidem](#) extended-release 12.5 mg (n=669) was associated with anxiety in 6.3% of patients compared with 2.6% with placebo (n=349), resulting in a discontinuation rate of 1.5% and 0.3%, respectively [38].

3.3.12.A.3] Complex mannerisms - behavior

a)] Complex behaviors including sleep driving, preparing and eating food, making phone calls, or having sexual intercourse while not fully awake and subsequently not remembering the performance of these activities has occurred following administration of sedative-hypnotics. These behaviors have occurred in sedative-hypnotic-naïve and sedative-hypnotic-experienced patients. Although determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) can not be made with certainty in most cases, any new behaviors should be immediately and carefully assessed. In cases of sleep-driving, strongly consider discontinuation of [zolpidem](#) due to the risk to the patient and others [1] [33] [34] [13] [38]. Risk of complex behaviors is increased with the use of alcohol and other CNS depressants and when the maximum recommended dose is exceeded [1] [33] [34] [13].

3.3.12.A.4] [Delirium](#)

a)] [Zolpidem](#) induced [delirium](#) with mania in a 67-year-old teacher with no significant psychiatric history who presented to the emergency room after 2 weeks of progressively worsening confusion, agitation, rapid speech, poor sleep, limited appetite, increased disorganization, and paranoid thoughts. Four days prior to hospitalization, she began to talk of the FBI following her and trying to harm her. Her affect was labile, agitated, and frightened, and thoughts were tangential and a flight of ideas. The patient was taking [zolpidem](#) 10 mg at bedtime for the past 6 weeks since being discharged from the hospital after knee replacement surgery [42].

b) Two and a half hours after receiving [zolpidem](#) 5 mg, an 86-year-old woman, who had sustained a [head trauma](#) 1 month prior to admission, became restless and would not follow directions of the nursing staff. She climbed over the bed rails and walked with an unsteady gait. She was oriented to person but not to time or place. She was given [haloperidol](#) 5 mg IM and restrained. With [haloperidol](#) 0.5 mg every 12 hours for 2 days, her symptoms resolved. This patient, in addition to being elderly and female, had hypoalbuminemia. All 3 factors can contribute to unusually high serum concentrations of [zolpidem](#) [43].

3.3.12.A.5] Depression

- a) Incidence: 1% to 2% [33] [34] [13] [38]
- b) Depression was reported in 2% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].
- c) During a three-week clinical trial, depression was reported in 2% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); this adverse effect occurred in 0% of patients in the placebo group (n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) extended-release 6.25 mg (n=99) or placebo (n=106), depression was reported in 1% compared with 0% in the placebo group [38].

3.3.12.A.6] Depression, worsening

- a) Worsening of depression, including [suicidal ideation](#), has been observed in association with sedative or hypnotic use. This effect has occurred primarily in depressed patients; the onset of any new behavioral sign or symptom that is of concern should be immediately evaluated [1] [34] [33] [13] [38].

3.3.12.A.7] Disturbance in thinking

- a) Abnormal thinking and changes in behavior have been reported with the use of sedative/hypnotics. These changes, similar to effects produced by alcohol and other CNS depressants, may include decreased inhibition (eg, aggressiveness and extroversion that seem out of character). Other behavior changes reported include bizarre behavior, agitation, and depersonalization [1] [33] [34] [13].

3.3.12.A.8] Dream disorder

- a) Incidence: 1% [33] [34] [13]
- b) Abnormal dreams were reported in 1% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.12.A.9] Euphoria

- a) Incidence: 1% or greater [33] [34] [13]
- b) Euphoria was reported in at least 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.12.A.10] Hallucinations

- a) Incidence: 0.1% to 7.4% [33] [34] [13] [38]
- b) Hallucinations were reported in 0.1% to 1% of 3660 patients receiving [zolpidem](#) tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

c) In an 8-week controlled study involving 201 pediatric patients (aged 6 to 17 years) with insomnia associated with ADHD, 7.4% of patients receiving [zolpidem](#) oral solution (n=136) compared with 0% of patients receiving placebo (n=65) experienced hallucinations [33] [34] [13].

d) During a three-week clinical trial, hallucinations were reported in 4% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102) compared with 0% in the placebo group (n=110) [38].

e) Three separate occurrences of visual hallucinations are described in a 23-year-old healthy female patient who was prescribed [zolpidem](#) for insomnia. On each occasion, visual hallucinations occurred after a short course of drug ([zolpidem](#) 10 mg nightly for 3 weeks, 5 days, and 4 days). This was followed by approximately a 50-hour free period, after which a 10-mg dose of [zolpidem](#) was taken for insomnia. Hallucinations, described as objects in the room appearing different and larger than normal, appeared 10 to 30 minutes later. The patient decreased her dose to 5 mg and experienced no complications [44].

f) Visual hallucinations were reported in 5 patients receiving [zolpidem](#); 4 patients receiving 5 to 20 mg and 1 patient receiving 60 mg. Most had been taking [zolpidem](#) for less than 1 week and all 5 were concomitantly using an antidepressant ([sertraline](#), [desipramine](#), [fluoxetine](#), [bupropion](#), or [venlafaxine](#)). Hallucinations lasted from 1 to 7 hours. The authors suggest that the hallucinations may have been due to an interaction between the SSRI and [zolpidem](#) [45].

g) A psychotic reaction following a single dose of [zolpidem](#) 10 mg was reported [46]. The patient was a 20-year-old female with [anorexia nervosa](#) who experienced visual hallucinations and macropsia 20 minutes after taking the drug. She then slept for 7 hours and woke up complaining of a "hangover." Her level of consciousness was normal during the period of hallucinations and had a full recall of the events. Rechallenge with a 5-mg dose one week later produced a similar episode with less intensity. The validity of this case-report is in question since possible hypnagogic visual illusions and/or hallucinations may also occur in a dream state, not only in [psychosis](#) [47].

3.3.12.A.11] [Memory impairment](#)

a) Incidence: 1% to 3% [33] [34] [13] [38]

b) Amnesia was reported in 1% of [chronic insomnia](#) patients receiving immediate-release [zolpidem](#) tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

c) During a three-week clinical trial, memory disorders, including amnesia, [anterograde amnesia](#), and [memory impairment](#), were reported in 3% of patients who received extended-release [zolpidem](#) 12.5 mg (n=102); the incidence was 0% in the placebo group (n=110). In another 3-week trial involving 205 elderly patients who received either [zolpidem](#) extended-release 6.25 mg (n=99) or placebo (n=106), memory disorder was reported in 1% compared with 0% in the placebo group [38].

d) Two patients experienced episodes of amnesia approximately one hour after taking 5 to 10 mg of [zolpidem](#). In both cases the subjects, a husband and wife, failed to recollect telephone conversations. It is possible that the [zolpidem](#) caused the amnesia but other contributing factors such as alcohol and travel fatigue cannot be excluded [48].

3.3.12.A.12] [Psychotic disorder](#)

a) A psychotic reaction following a single dose of [zolpidem](#) 10 mg was reported [46]. The patient was a 20-year-old female with [anorexia nervosa](#) who experienced visual hallucinations and macropsia 20 minutes after taking the drug. She then slept for 7 hours and woke up complaining of a "hangover." Her level of consciousness was normal during the period of hallucinations and had a full recall of the events. Rechallenge with a 5-mg dose one week later produced a similar episode with less intensity. The validity of this case-report is in question since possible hypnagogic visual illusions and/or hallucinations may also occur in a dream state, not only in [psychosis](#) [47].

b) Two cases of zolpidem-induced psychosis have been reported in elderly women. The first was a 71-year-old woman who took zolpidem 20 mg on 2 occasions [49]. Afterwards her husband reported that she saw people outside of the window and began talking nonsensically. She could not recall these events. The second was a 74-year-old woman who was given zolpidem 20 mg prior to a magnetic resonance imaging test [50]. Within 1 hour she began babbling incoherently and was confused. After 2 hours, she developed auditory-visual hallucinations, delusions, and psychomotor agitation. This lasted for 3 hours.

3.3.12.A.13] Suicidal thoughts

a) Worsening of depression, including suicidal ideation, has been observed in association with sedative or hypnotic use. This effect has occurred primarily in depressed patients; the onset of any new behavioral sign or symptom that is of concern should be immediately evaluated [1] [38] [34] [33] [13].

3.3.13] Renal Effects

3.3.13.A] Zolpidem Tartrate

3.3.13.A.1] Urinary tract infectious disease

- a) Incidence: 1% or greater [33] [34] [13]
- b) Urinary tract infection was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.15] Respiratory Effects

3.3.15.A] Zolpidem Tartrate

3.3.15.A.1] Hiccoughs

- a) Incidence: 1% or greater [33] [34] [13]
- b) Hiccup was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.15.A.2] Hypoxia

a) The effect of zolpidem 10 mg nightly on respiration was studied in 10 elderly female patients. Respiratory monitoring with an inductance plethysmograph and pulse oximeter revealed no significant increases in severity, frequency, or duration of hypoxia as compared with placebo [41].

3.3.15.A.3] Pharyngitis

- a) Incidence: 3% [33] [34] [13]
- b) Pharyngitis was reported in 3% of chronic insomnia patients receiving immediate-release zolpidem tartrate 5 mg or 10 mg per night (n=152) compared with 1% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [33] [34] [13].

3.3.15.A.4] Sinusitis

- a) Incidence: 4% [33] [34] [13]

b) Sinusitis was reported in 4% of chronic insomnia patients receiving immediate-release zolpidem tartrate 5 mg or 10 mg per night (n=152) compared with 2% of patients receiving placebo (n=161) during long-term efficacy trials (28 to 35 nights) [13] [33] [34].

3.3.15.A.5] Upper respiratory infection

a) Incidence: 1% or greater [33] [34] [13]

b) Upper respiratory tract infection was reported in at least 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.16] Other

3.3.16.A] Zolpidem Tartrate

3.3.16.A.1] Angioedema

a) Incidence: rare [34] [33] [13] [38]

b) Cases of angioedema involving the tongue, glottis, or larynx, some fatal, have been reported rarely in patients following the first or subsequent doses of sedative-hypnotics, including zolpidem. Additional symptoms suggestive of anaphylaxis, including dyspnea, throat closing, or nausea and vomiting, have been reported. Some patients with these symptoms have presented to the emergency department. Do not rechallenge patients who have experienced angioedema following zolpidem treatment [1] [34] [33] [13] [38].

3.3.16.A.2] Drug dependence

a) Rebound insomnia has occurred on the first night after discontinuation of the drug [52].

b) A 46-year-old man, with a history of polysubstance abuse since a teenager, developed tolerance and dependence to zolpidem, prescribed for stress-related insomnia 2 years earlier. For the first 18 months, the patient reported taking 5 to 10 mg at bedtime. After a few months, he began taking 1.25 to 2.5 mg in the evening and then 5 mg several times during the day to decrease anxiety, with an estimate of 400 mg daily. Furthermore, several months prior to hospital admission, he began taking lorazepam 1 mg every 8 hours, consuming several tablets a day, up to 20 tablets over one weekend. He tapered the lorazepam one month prior to hospital admission. Upon admission, he presented with tremors, sweats, chills, shakiness, and headache. To ease the zolpidem withdrawal, he received a 7-day detoxification protocol of diazepam (day 1, 10 mg every 4 hours for 1 day; day 2, 10 mg every 6 hours for 1 day; day 3, 5 mg every 6 hours for 1 day; day 4, 2 mg every 6 hours for 1 day, then every 8 hours for 1 day, followed by every 12 hours for 1 day and finally every 24 hours for 1 day). His anxiety was managed with nefazodone 600 mg divided throughout the day; although, he reports 3 to 4 hours of insomnia nightly [53].

c) A 44-year-old woman developed tolerance and dependence to zolpidem after experiencing a stressful life event [54]. She self-administered zolpidem 50 to 100 mg/day and occasionally up to 300 mg/day. She alternated abuse and abstinence of the drug over 3 years. She experienced an altered state of consciousness and hallucinations while abusing the drug, and anxiety, dysthymic mood, irritability, lack of energy, and difficulty concentrating while abstaining. She was eventually hospitalized while the zolpidem was tapered off and treated with fluoxetine 60 mg plus clorazepate 30 mg.

d) Dependence and tolerance with zolpidem were reported in a 33-year-old man. The patient was initially prescribed 10 mg at bedtime but he subsequently progressively increased the dose to 300 to 400 mg daily after experiencing anxiety, restlessness and insomnia. Abrupt discontinuation of

zolpidem led to withdrawal symptoms (rebound insomnia, anxiety, agitation, and seizures) which were attenuated by reinstating the drug [55].

e) Two patients with major psychiatric disorders suffered from early wakening (after 2 to 3 hours) during zolpidem therapy and as a result increased their dose to 50 to 100 mg; withdrawal symptoms (anxiety, tremor, sweating, tachycardia, tachypnea, nausea, gastric and abdominal pain) were apparent during the day and one patient, after suspected voluntary overdosing, had a generalized self-limiting seizure [56]. It has been questioned whether or not some of these symptoms may have been due to the preexisting psychiatric disorders [47].

3.3.16.A.3] Falls

a) A fall rate of 3% was reported for patients who received zolpidem (n=4962) compared with 0.7% for patients who were prescribed, but not administered, zolpidem (n=11,358) in a retrospective cohort study of adult non-ICU hospitalized patients. With an absolute increase in risk of falling of 1.8% for patients who received zolpidem as compared with all other adult hospitalized patients, the calculated number needed to harm is 55. After adjusting for age, gender, insomnia, delirium status, dose of zolpidem, Charlson comorbidity index score, fall risk score, length of hospital stay, presence of visual impairment, gait abnormalities, and dementia or cognitive impairment, patients who received zolpidem were associated with a significantly increased risk of falling (adjusted odds ratio, 4.37; 95% CI, 3.34 to 5.76) [51].

3.3.16.A.4] Fatigue

a) Incidence: 0.1% to 3% [1] [33] [34] [13] [38]

b) Fatigue was reported in 1% of patients who took zolpidem sublingual tablets 3.5 mg (Intermezzo(R); n=150) and 0% of patients who took placebo (n=145) on an as needed basis for middle-of-the-night awakenings, in a 4-week, double-blind, placebo-controlled, outpatient study of adult patients with insomnia. Zolpidem sublingual tablets were taken on 62% of the study nights. Adverse reaction incidence rates were similar in patients receiving zolpidem 1.75 mg during a double-blind, placebo-controlled, 3-period crossover sleep laboratory study (n=82) [1].

c) During a three-week clinical trial, fatigue occurred in 3% of patients who received extended-release zolpidem 12.5 mg (n=102); this adverse effect occurred in 2% of patients in the placebo group (n=110) [38].

d) Fatigue was reported in 0.1% to 1% of 3660 patients receiving zolpidem tartrate at any dose during pre-approval clinical trials conducted in the United States, Europe, and Canada. Adverse event causality could not be determined [33] [34] [13].

3.3.16.A.5] Influenza-like illness

a) Incidence: 2% [33] [34] [13]

b) Flu-like symptoms were reported in 2% of chronic insomnia patients receiving immediate-release zolpidem tartrate 5 mg or 10 mg per night (n=152) compared with 0% of patients receiving placebo (n=161) for 28 to 35 nights during long-term efficacy trials [33] [34] [13].

3.3.16.A.6] Withdrawal sign or symptom

a) Withdrawal symptoms, including convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, mild dysphoria, and insomnia have been reported with abrupt discontinuation of sedative/hypnotics. Other withdrawal effects reported include fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, panic attack, nervousness, and abdominal discomfort [1] [33] [34] [13].

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

A) **Teratogenicity/Effects in Pregnancy**

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

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential **risk to the fetus**.

2) Australian Drug Evaluation Committee's (ADEC) Category: B3

a) Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Adequate and well-controlled studies with **zolpidem** have not been conducted in pregnant women. Although specific observations with **zolpidem** have not been reported, use of other sedative/hypnotics during pregnancy has resulted in neonatal withdrawal symptoms and/or flaccidity [114] [34] [33]. One study of women who received **zolpidem** during pregnancy found significant risks for preterm, cesarean, low birth weight, small for gestational age births, but not congenital abnormalities, compared with controls [111]. **Zolpidem** was present in the cord blood of a neonate born to a 30-year-old woman who was exposed to **zolpidem** during pregnancy [113]. It is recommended that **zolpidem** be used during pregnancy only if the potential benefit to the mother outweighs the potential **risk to the fetus** [114] [34] [33].

5) Literature Reports

a) In an adjusted analysis, a retrospective Taiwanese study of women (mean age 29.7 years) who received **zolpidem** during pregnancy (n=2497) found significant risks for preterm, cesarean, low birth weight (LBW), small for gestational age (SGA) births, but not congenital abnormalities, compared with controls (n=12,485). Overall incidence of LBW (7.61%; odds ratio (OR) 1.39 (95% confidence interval (CI), 1.17 to 1.64); p less than 0.001), **preterm birth** (10.01%; OR 1.49 (95% CI, 1.28 to 1.74); p less than 0.001), SGA (19.94%; OR 1.34 (95% CI, 1.2 to 1.49); p less than 0.001), and cesarean births (46.86%; OR 1.74 (95% CI, 1.59 to 1.9); p less than 0.001) was higher in women who received **zolpidem** compared with 5.19%, 6.3%, 15.06%, and 33.46%, respectively, of controls tracked across all trimesters (n=12,485). The risk of low birth weight with first-trimester **zolpidem** exposure (n=535) was not significant, but **preterm birth** (10.28%), SGA (20.19%), and cesarean births (47.66%) were all higher than controls (OR 1.48 (95% CI, 1.1 to 1.98), p less than 0.01; OR 1.36 (95% CI, 1.09 to 1.69) p less than 0.01; and OR 1.73 (95% CI, 1.45 to 2.06), p less than 0.001, respectively). Risks of second- or third-trimester **zolpidem** exposure (n=1962) remained significantly higher than controls for LBW (7.75%; OR 1.42 (95% CI, 1.18 to 1.71), p less than 0.001), **preterm**

birth (9.94%; OR 1.49 (95% CI, 1.26 to 1.77), p less than 0.001), SGA (19.88%; OR 1.33 (95% CI, 1.18 to 1.5), p less than 0.001), and cesarean births (46.64%; OR 1.75 (95% CI, 1.58 to 1.93), p less than 0.001) [111].

b)) Zolpidem treatment between 30 and more than 180 days significantly increased risks of low birth weight (LBW), preterm, small for gestational age (SGA), and cesarean births, but not congenital abnormalities, compared with controls (n=12,485). Significantly increased risks of LBW (7.19%; adjusted odds ratio (AOR) 1.3 (95% confidence interval (CI), 1.05 to 1.62), p less than 0.05), preterm (9.65%; AOR 1.46 (95% CI, 1.2 to 1.76), p less than 0.001), SGA (18.48%; AOR 1.21 (95% CI, 1.05 to 1.4), p less than 0.01), and cesarean births (46%; AOR 1.72 (95% CI, 1.52 to 1.92), p less than 0.001) were reported for **zolpidem** therapy between 30 and 90 days (n=1461) compared with 5.19%, 6.3%, 15.06%, and 33.46%, respectively, of controls (n=12,485). Significant risks of LBW (8.29%; AOR 1.52 (95% CI, 1.1 to 2.11), p less than 0.05), SGA (22.6%; AOR 1.57 (95% CI, 1.27 to 1.94), p less than 0.001), and cesarean births (45.57%; AOR 1.66 (95% CI, 1.34 to 1.98), p less than 0.001) were reported for **zolpidem** therapy between 90 to 180 days (n=531), but with no significantly increased risk of **preterm birth**. Significantly increased risks of LBW (8.12%; AOR 1.48 (95% CI, 1.06 to 2.07), p less than 0.05), preterm (11.68%; AOR 1.74 (95% CI, 1.31 to 2.32), p less than 0.001), SGA (21.39%; AOR 1.48 (95% CI, 1.19 to 1.85), p less than 0.001), and cesarean births (50.69%; AOR 1.9 (95% CI, 1.31 to 2.62), p less than 0.001) were reported with more than 180 days of **zolpidem** therapy (n=505) [111].

c)) A series of observational cohort studies suggested that **zolpidem** did not increase the rate of congenital anomalies when used during pregnancy. Of 45 pregnant women who took the drug, 24 discontinued the drug before the last menstrual period, 18 were exposed during the first trimester, and one during the second or third trimester; exposure for two was unknown. Of the 18 exposed during the first trimester, there were 10 births without congenital anomalies, two **spontaneous abortions**, and six intentionally terminated pregnancies [112].

d)) A case report described presence of **zolpidem** in the cord blood of a neonate born to a 30-year-old woman who was exposed to **zolpidem** during pregnancy. At gestation week 27, she had presented with presumed **placental abruption** which was stabilized. However, she began experiencing withdrawal symptoms of nervousness and anxiety, despite treatment with **zolpidem** 5 to 10 mg/night for inability to sleep. Based on family member accounts, the woman had been suspected of abusing **zolpidem** (10 to 15 tablets/night). **Placenta previa** or abruption was not seen on **ultrasonography** and, following a psychology consult, the patient was prescribed **zolpidem** 15 mg/night and discharged after 7 days. **Zolpidem** was tapered down to 10 mg/night 2 weeks later. At week 30, the patient showed up with a complaint of decreased fetal movement. After physical examination and tests, weekly antepartum testing was scheduled and the patient was discharged. At week 34, the patient returned with minor vaginal bleeding and periorbital headache. She denied using **zolpidem** at this time and, after ruling out **pyelonephritis** and **urinary tract infection**, was given **hydrocodone/acetaminophen** for the headache and discharged. A 3.95 kg female baby was delivered via normal vaginal delivery under **epidural anesthesia** at week 38. No complications occurred in both mother and neonate, whose Apgar score was 8-9. Also, no withdrawal symptoms were noted in the neonate over the next 48 hours. Cord blood, taken approximately 20 minutes after delivery, showed a **zolpidem** level of 41 ng/mL indicating that the patient may have taken **zolpidem** up until time of delivery. However, the time from her last dose and the actual amount of **zolpidem** taken were unknown [113].

e)) A dose-related decrease in fetal skull ossification was demonstrated when pregnant rats were given oral **zolpidem** base in doses of 20 mg/kg or 100 mg/kg (approximately 24 and

120 times the maximum recommended human dose (MRHD) on a mg/m(2) basis, respectively) during organogenesis; no adverse effects were seen with 4 mg/kg (approximately 5 times the MRHD on a mg/m(2) basis). An increase in embryo-fetal death and incomplete fetal skeletal (sternebrae) ossification occurred when pregnant rabbits were dosed with 16 mg/kg of [zolpidem](#) base (approximately 40 times the MRHD on a mg/m(2) basis); no adverse effects were seen with 1 mg/kg or 4 mg/kg doses (approximately 2.5 and 10 times the MRHD on a mg/m(2) basis, respectively). A decrease in offspring growth and survival was noted when pregnant rats were given oral [zolpidem](#) base in doses of 20 mg/kg and 100 mg/kg (approximately 24 and 120 times the MRHD on a mg/m(2) basis, respectively) during the latter stages of pregnancy and throughout lactation; no adverse effects occurred with 4 mg/kg (approximately 5 times the MRHD on a mg/m(2) basis) [34] [33].

B) Breastfeeding

1) American Academy of Pediatrics Rating: Maternal medication usually compatible with breastfeeding.

2) Micromedex Lactation Rating: Infant risk is minimal.

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

3) Clinical Management

a) Only a very small amount of maternally administered [zolpidem](#) is excreted into human breast milk. However, [zolpidem](#) has not been studied in lactating women and the infant effects from exposure via nursing are unknown. Notably, the pharmacokinetics (high protein binding, inactive metabolites, short half-life, lack of accumulation with daily dosing) do not favor substantial excretion into breast milk and neonatal absorption. While the American Academy of Pediatrics considers [zolpidem](#) compatible with breastfeeding [115], the manufacturer advises caution if [zolpidem](#) is administered to nursing mothers [114] [34] [33].

4) Literature Reports

a) One study described five lactating women given [zolpidem](#) 20 mg (twice the current maximum recommended hypnotic dose) followed by serum and breast milk sampling. At three hours post-dose, the amount of [zolpidem](#) in milk measured 0.76 to 3.88 micrograms (0.004% to 0.019% of the maternal dose) and the milk-to-plasma (M/P) concentration ratio was 0.13. The amount of [zolpidem](#) in the subsequent samples (13 and 16 hours after the dose) was less than the detectable limit of 0.5 micrograms per liter [116].

5) Drug Levels in Breastmilk

a) [Zolpidem](#) Tartrate

1) Parent Drug

a) Percent Adult Dose in Breastmilk

1) 0.004% to 0.019% [114] [33] [13]

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Alprazolam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.B] Amiodarone

- 1) Interaction Effect: increased CYP1A2, CYP2C9, CYP2D6, CYP3A4, or P-glycoprotein substrate exposure
- 2) Summary: Concomitant use of [amiodarone](#) (an inhibitor of CYP1A2, CYP2C9, CYP2D6, CYP3A4, and of P-glycoprotein efflux transport) and drugs that are substrates of these metabolic enzymes and transporter may increase the exposure of these drugs. As [amiodarone](#) has a variable and long half-life, potential drug interaction may occur even after [amiodarone](#) is discontinued [95]. If [amiodarone](#) is used concomitantly (or after [amiodarone](#) is discontinued) with any of these drugs, use with caution, monitor for increased adverse effects, and consider dose adjustment as appropriate.
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [amiodarone](#) (an inhibitor of CYP1A2, CYP2C9, CYP2D6, CYP3A4, and of P-glycoprotein efflux transport) and drugs that are substrates of these metabolic enzymes and transporter may increase the exposure of these drugs [95]. If [amiodarone](#) is used concomitantly with any of these drugs, use with caution, monitor for increased adverse effects, and consider dose adjustment as appropriate.
- 7) Probable Mechanism: inhibition of CYP1A2-, CYP2C9-, CYP2D6-, or CYP3A4-mediated metabolism, or P-glycoprotein-mediated efflux transport by [amiodarone](#)

3.5.1.C] Bupropion

- 1) Interaction Effect: an increased risk of hallucinations
- 2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [100].
- 3) Severity: moderate
- 4) Onset: delayed

- 5) Substantiation: probable
- 6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin-reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [99].

3.5.1.D) [Buspirone](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.E) [Butabarbital](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.F) [Carbamazepine](#)

- 1) Interaction Effect: decreased [zolpidem](#) plasma concentrations
- 2) Summary: The concomitant use of [carbamazepine](#) with [zolpidem](#) may result in decreased efficacy of [zolpidem](#) due to a reduction in mean plasma concentrations of [zolpidem](#) by [carbamazepine](#). A

pharmacokinetic study of 18 healthy, nonsmoking adult males demonstrated that concurrent use of **carbamazepine** and **zolpidem** increased the clearance of **zolpidem** and lowered its bioavailability by approximately 57% due to induction of CYP3A4-, CYP2C9-, and CYP1A2-mediated **zolpidem** metabolism by **carbamazepine** [57].

3) Severity: major

4) Onset: unspecified

5) Substantiation: established

6) Clinical Management: The concomitant use of **carbamazepine** with **zolpidem** may result in decreased efficacy of **zolpidem** due to a reduction in mean plasma concentrations of **zolpidem** by **carbamazepine** [57].

7) Probable Mechanism: induction of CYP3A4-, CYP2C9-, and CYP1A2-mediated **zolpidem** metabolism by **carbamazepine**

8) Literature Reports

a) Concomitant use of **carbamazepine** and **zolpidem** increased the clearance of **zolpidem** and lowered its bioavailability by approximately 57% in a **pharmacokinetic study** of 18 healthy, nonsmoking adult males. The study involved 2 periods: in period 1, each subject received a single dose of **zolpidem** 5 mg and in period 2, each subject received a single dose of **zolpidem** 5 mg plus **carbamazepine** 400 mg. Between the two periods, subjects were treated with a single daily dose of **carbamazepine** 400 mg for 15 days, and all drugs were administered in the fasted state in the morning. Mean C_{max} in the **zolpidem** alone treatment group was 59 +/- 24 nanograms (ng)/mL compared with 35 +/- 15 ng/mL in the **zolpidem/carbamazepine** group (p less than 0.0001). The AUC (0 to infinity) was 234.9 +/- 165.4 and 101.5 +/- 59 ng x hour/mL, respectively (p less than 0.0001). The elimination half-life was also significantly decreased from 2.3 +/- 0.7 hours with **zolpidem** administered alone to 1.6 +/- 0.5 hours after coadministration with **carbamazepine** (p less than 0.0001) [57].

3.5.1.G] 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 [72] [73]. 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 [72] [73]. 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.H] Chlordiazepoxide

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 [103].

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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.I) [Chlorpromazine](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.J) [Ciprofloxacin](#)

- 1) Interaction Effect: increased [zolpidem](#) plasma concentrations
- 2) Summary: A [pharmacokinetic study](#) of 18 healthy, nonsmoking men demonstrated that concurrent use of [ciprofloxacin](#) and [zolpidem](#) led to a 46% increase in [zolpidem](#) bioavailability due to probable inhibition of CYP3A4- and CYP1A2-mediated [zolpidem](#) metabolism. Increase in [zolpidem](#) t(1/2) and C_{max} and decrease in clearance were also noted, but were not clinically significant. [68]. Use caution if coadministration of [ciprofloxacin](#) is necessary.
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of [ciprofloxacin](#) and [zolpidem](#) may result in reduced clearance and increased plasma concentrations of [zolpidem](#) [68]. Use caution if coadministration of [ciprofloxacin](#) is required.
- 7) Probable Mechanism: inhibition of CYP3A4- and CYP1A2-mediated [zolpidem](#) metabolism by [ciprofloxacin](#)
- 8) Literature Reports

a) Concomitant use of [ciprofloxacin](#) and [zolpidem](#) led to a 46% increase in [zolpidem](#) bioavailability in a pharmacokinetic (PK) study of 18 healthy, nonsmoking men. The suspected mechanism of interaction was inhibition of CYP3A4- and CYP1A2-mediated [zolpidem](#) metabolism by [ciprofloxacin](#). In study period 1, subjects received a single dose of [zolpidem](#) 5 mg for reference PK values. In period 2, subjects received a single dose of [zolpidem](#) 5 mg plus [ciprofloxacin](#) 500 mg. In between the 2 periods, subjects received [ciprofloxacin](#) 500 mg daily for 5 days. Clinically significant changes in PK parameters were likely if the 90% confidence interval (CI) of the geometric mean ratio (test value to reference value) fell outside the bioequivalence range of 0.8 to 1.25. Following concomitant administration of [ciprofloxacin](#), a statistically and clinically significant increase in [zolpidem](#) AUC was observed. [Zolpidem](#) AUC (0 to infinity) increased from

300.2 +/- 115.5 to 438.1 +/- 142.6 nanograms x hr/mL (p less than 0.0001), and the 90% CI of the geometric mean ratio was 1.34 to 1.66. While a statistically significant increase in **zolpidem** mean C_{max} occurred from 75.73 +/- 28.34 to 80.58 +/- 22.4 nanograms/mL (p=0.0076), this increase was not clinically significant (90% CI, 0.96 to 1.26). Increase in **zolpidem** T_{max} was deemed clinically significant. Decrease in clearance and increase in elimination half-life were statistically significant, but clinical significance was not provided [68].

3.5.1.K] Clonazepam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.L] Clorazepate

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.M] Cobicistat

- 1) Interaction Effect: increased **zolpidem** exposure
- 2) Summary: Cobicistat is a strong CYP3A4 inhibitor. Caution is advised when using cobicistat together with a CYP3A4 substrate such as **zolpidem** as this may result in elevated plasma concentrations of **zolpidem**. If concomitant use is required, **zolpidem** should be initiated at a lower dose [90] and clinical monitoring is recommended [91]. A dose reduction for **zolpidem** may be required [90] [91].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Caution is advised when using cobicistat together with a CYP3A4 substrate such as **zolpidem** as this may result in elevated plasma concentrations of **zolpidem**. If concomitant use

is required, initiate [zolpidem](#) at a lower dose [90]. Clinical monitoring is recommended [91] and a dose reduction for [zolpidem](#) may be required [90] [91].

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

3.5.1.N] 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 [70].

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 [70].

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 [70].

3.5.1.O] 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 [59].

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 [59].

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 [59].

3.5.1.P] 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 [71].

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 [71].

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

3.5.1.Q] [Desipramine](#)

1) Interaction Effect: an increased risk of hallucinations

2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [97].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.

7) Probable Mechanism: unknown

8) Literature Reports

a) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin-reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [96].

3.5.1.R] [Dexmedetomidine](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.S] [Diazepam](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.T] [Diphenhydramine](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.U] [Doxylamine](#)

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 [103].

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 [103].

7J) Probable Mechanism: additive effects

3.5.1.V] Eslicarbazepine Acetate

1J) Interaction Effect: decreased exposure of CYP3A4 substrates

2J) Summary: Concurrent administration of eslicarbazepine acetate (a CYP3A4 inducer) and a CYP3A4 substrate may decrease the exposure of the CYP3A4 substrate. If used concomitantly [62], use caution and monitor the patient closely.

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [62], use caution and monitor the patient closely.

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

3.5.1.W] Estazolam

1J) Interaction Effect: an increase in central nervous system depressant effects

2J) 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 [103].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [103].

7J) Probable Mechanism: additive effects

3.5.1.X] Eszopiclone

1J) Interaction Effect: an increase in central nervous system depressant effects

2J) 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 [103].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) 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 [103].

7J) Probable Mechanism: additive effects

3.5.1.Y] Ethchlorvynol

1J) 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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.Z| [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 [88]. 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](#) [89]. 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 [88].

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 [88].

7) Probable Mechanism: additive CNS depression

3.5.1.AA| [Flumazenil](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AB| [Fluoxetine](#)

- 1J) Interaction Effect: an increased risk of hallucinations
- 2J) Summary: Short-term combined therapy with [fluoxetine](#) and [zolpidem](#) was determined to be safe by a study involving 29 healthy women. After a single dose of [zolpidem](#) followed by one washout day, the subjects were given a daily dose of [fluoxetine](#) on days three through 27, then [zolpidem](#) was added each evening on days 28 through 32. There were no significant changes in either [fluoxetine](#) or [zolpidem](#) plasma concentrations, and both medications were tolerated well, either individually or combined [86]. However, the publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [87].
- 3J) Severity: moderate
- 4J) Onset: delayed
- 5J) Substantiation: theoretical
- 6J) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.
- 7J) Probable Mechanism: unknown
- 8J) Literature Reports

aJ) A study conducted by Lorex Pharmaceuticals and Boston Research and Science Consulting demonstrates the safety of concomitant short-term therapy with [fluoxetine](#) and [zolpidem](#). In this study, 29 healthy female volunteers were given a single evening dose of [zolpidem](#) 10 mg, followed by one washout day. This was followed by a daily morning dose of [fluoxetine](#) 20 mg on days 3 through 27. On days 28 through 32, a daily evening dose of [zolpidem](#) was added. Steady state plasma concentrations of [fluoxetine](#) and norfluoxetine were reached on day 24 of [fluoxetine](#) dosing as determined by serial venous blood sampling. There were no significant differences in area under concentration curve (AUC), peak concentration (C_{max}), or time to reach peak concentration (T_{max}) after one or five consecutive doses of [zolpidem](#) in conjunction with [fluoxetine](#) administration. The following pharmacokinetic mean parameters were observed for [zolpidem](#): AUC 917.04 ng/hr/mL on day 28, 978.77 ng/hr/mL on day 32, C_{max} 167.94 ng/mL on day 28, 175.91 ng/mL on day 32, T_{max} 1.67 hr on day 28, 1.54 hr on day 32. For [fluoxetine](#) the following were noted: AUC 2674.53 ng/hr/mL on day 27, 2879.63 ng/hr/mL on day 32, C_{max} 133.48 ng/mL on day 27, 142.23 ng/mL on day 32, T_{max} 8.28 hr on day 27, 9.04 hr on day 32. The only statistically significant difference was a higher half-life value for [zolpidem](#) on day 32, the fifth consecutive dose of [zolpidem](#) in the presence of [fluoxetine](#) [84].

bJ) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [85].

3.5.1.AC] [Flurazepam](#)

- 1J) Interaction Effect: an increase in central nervous system depressant effects
- 2J) 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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AD] [Fluvoxamine](#)

1) Interaction Effect: decreased [zolpidem](#) clearance and increased exposure

2) Summary: Concomitant use of [fluvoxamine](#), a potent CYP1A2 inhibitor, and moderate CYP3A4 and CYP2C9 inhibitor [78] [79], together with [zolpidem](#), a CYP3A4, CYP2C9, and CYP1A2 substrate, significantly increased [zolpidem](#) Cmax, AUC, and half-life (150% increased exposure) in a pharmacokinetic trial with healthy volunteers (n=20) [78]. Concomitant therapy with [fluvoxamine](#) may increase the risk of zolpidem-related side effects and dose adjustments may be warranted during coadministration.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Concomitant use of [fluvoxamine](#) and [zolpidem](#) increased [zolpidem](#) exposure by approximately 150% [78]. Concomitant therapy may increase the risk of zolpidem-related side effects and dose adjustments may be warranted during coadministration.

7) Probable Mechanism: inhibition of CYP3A4-, CYP2C9, and CYP1A2-mediated metabolism of [zolpidem](#) by [fluvoxamine](#)

8) Literature Reports

a) The [zolpidem](#) Cmax, total AUC, and half-life were significantly increased after pretreatment with [fluvoxamine](#) in a pharmacokinetic trial with 20 healthy male volunteers (22 to 30 years old). Participants were given a single dose of [zolpidem](#) 5 mg (day 1), followed by 6 days of [fluvoxamine](#) 100 mg/day (days 2 to 7), and a second dose of [zolpidem](#) 5 mg together with [fluvoxamine](#) 100 mg on day 8. The mean Cmax of [zolpidem](#) was 56.4 +/- 25.6 nanograms (ng)/mL on day 1 and 67.3 +/- 25.8 ng/mL after pretreatment with [fluvoxamine](#) (p=0.005; 90% CI, 1.10 to 1.37), and the [zolpidem](#) AUC(0 to infinity) increased by approximately 150% from 200.9 +/- 116.8 ng x hr/mL to 512 +/- 354.6 ng x hr/mL after pretreatment (p less than 0.0001; 90% CI, 2.14 to 2.71). The half-life was 2.24 +/- 0.8 hours with [zolpidem](#) alone compared with 4.99 +/- 2.92 hours with concomitant [fluvoxamine](#) (p less than 0.0001). Chronic use of concomitant [zolpidem](#) and [fluvoxamine](#) might lead to enhanced adverse effects associated with [zolpidem](#) [78].

3.5.1.AE] [Fospropofol](#)

1) Interaction Effect: additive cardiorespiratory effects

2) Summary: Concomitant use of fospropofol and [zolpidem](#) may result in additive cardiorespiratory effects due to the sedative action of both drugs [74]. 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 [zolpidem](#) are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.AF] [Halazepam](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AG] [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 [98].

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 [98].

7) Probable Mechanism: additive CNS depression

3.5.1.AH] [Hydromorphone](#)

1) Interaction Effect: an increase in CNS or [respiratory depression](#)

2) Summary: The concomitant use of [hydromorphone](#) and other CNS depressants, such as sedatives and hypnotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [hydromorphone](#) and a sedative or hypnotic together, dose reduction of one or both of the medications should be considered [106].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Concomitant use of [hydromorphone](#) and other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered [106].
- 7) Probable Mechanism: additive effects

3.5.1.AJ [Hydroxyzine](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AJ [Ketoconazole](#)

- 1) Interaction Effect: increased plasma concentrations and pharmacodynamic effects of [zolpidem](#)
- 2) Summary: A randomized, double-blind, 5-way crossover study of 12 healthy volunteers demonstrated decreased clearance and increased plasma concentrations of [zolpidem](#) when coadministered with [ketoconazole](#). Mean clearance was reduced to 64% when compared to [zolpidem](#) plus placebo, and mean area under the concentration-time curve (AUC) was increased by a factor of 1.83. [Zolpidem](#) coadministered with [itraconazole](#) or [fluconazole](#) produced only small changes in kinetics and dynamics of [zolpidem](#) [67].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: If concurrent administration of [zolpidem](#) and [ketoconazole](#) is necessary, patients should be monitored for effects such as decreased concentration and somnolence.
- 7) Probable Mechanism: impaired metabolism of [zolpidem](#)
- 8) Literature Reports

a) Increased plasma concentrations and pharmacodynamic effects of [zolpidem](#) when coadministered with [ketoconazole](#) were demonstrated in a randomized, double-blind, 5-way crossover study of 12 healthy volunteers. The study involved five treatment protocols: (a) [zolpidem](#) placebo plus azole placebo, (b) 5 mg [zolpidem](#) plus azole placebo, (c) [zolpidem](#) plus [ketoconazole](#), (d) [zolpidem](#) plus [itraconazole](#), and (e) [zolpidem](#) plus [fluconazole](#). The mean clearance of [zolpidem](#) was decreased from 422 mL/min for the (b) treatment group to 250 mL/min for the (c) treatment group. Changes also were noted in the elimination half-life ($t_{1/2}$) from 1.86 to 2.41 h, and area under the concentration-time curve (AUC) from 254 to 424 ng/mL/h, respectively. The [ketoconazole](#) group also demonstrated pharmacodynamic changes as expressed by EEG beta amplitude increases and impairment of DSST (digit-symbol substitution test) scores, as well as slight impairment of delayed recall. There were no significant changes in kinetics or dynamics of [zolpidem](#) in the other azole treatment groups [66].

3.5.1.AK] Lorazepam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AL] 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 [92] and use with caution [93].
- 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 [92] and use with caution [93].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AM] 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](#) [80] [81] [82] 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](#) [80] [81] [82] 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.AN] Meprobamate

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AO] Midazolam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AP] 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 [101] 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 [101] 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.AQ] Oxazepam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AR] [Oxycodone](#)

- 1) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2) Summary: Concomitant use of [oxycodone](#) with other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. 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 [60] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [61].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [oxycodone](#) with other CNS depressants, such as sedatives or hypnotics, 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 [60] and initiate extended-release [oxycodone](#) hydrochloride/[acetaminophen](#) at one-half the usual dose [61].
- 7) Probable Mechanism: additive effects

3.5.1.AS] [Pentobarbital](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.AT] [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 [94].

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 [94].

7) Probable Mechanism: additive CNS depression

3.5.1.AU] Phenobarbital

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AV] Piperaquine

1) Interaction Effect: increased exposure of CYP3A4 substrates

2) Summary: Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised with administration of a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy [102]. If concomitant administration is required, use caution and monitor the patient closely.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concurrent administration of piperaquine (a CYP3A4 inhibitor) and a CYP3A4 substrate may increase the exposure of the CYP3A4 substrate. Due to the long half-life of piperaquine, caution is advised with administration of a CYP3A4 substrate for up to 3 months after discontinuation of piperaquine therapy [102]. If concomitant administration is required, use caution and monitor the patient closely.

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

3.5.1.AW] Prazepam

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AX] [Primidone](#)

1) Interaction Effect: decreased exposure of CYP3A4 substrates

2) Summary: [Primidone](#) is metabolized to [phenobarbital](#) [58] (a strong CYP3A4 inducer). Concomitant use of [primidone](#) with certain CYP3A4 substrates may result in decreased exposure of the CYP3A4 substrate and should be avoided if clinically possible. If concomitant administration is required, use caution and monitor the patient closely.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use if clinically possible. If coadministration is required, use caution and monitor the patient closely.

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

3.5.1.AY] [Promethazine](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.AZ] [Propofol](#)

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 [103].

- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.BA| [Quazepam](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.BB| [Ramelteon](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.BC| [Rifampin](#)

- 1) Interaction Effect: decreased plasma concentration and pharmacodynamic effect of [zolpidem](#)
- 2) Summary: [Rifampin](#) significantly reduced the plasma levels and pharmacodynamic effect of [zolpidem](#) in 8 healthy females in a randomized, crossover study [108].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: If [rifampin](#) is given concurrently with [zolpidem](#) patients should be monitored for decreased effectiveness of [zolpidem](#).
- 7) Probable Mechanism: increased metabolism of [zolpidem](#)

8) Literature Reports

a) **Rifampin** significantly reduced the plasma levels and pharmacodynamic effect of **zolpidem** in 8 healthy females in a randomized, crossover study. Subjects were randomized to receive either **rifampin** 600 mg once daily or placebo for 5 days. On the sixth day a single dose of **zolpidem** 20 mg was administered, 17 hours after the last dose of **rifampin** or placebo. After pretreatment with **rifampin**, the elimination half-life of **zolpidem** was significantly decreased from 2.5 hours to 1.6 hours. The area under the plasma concentration curve and the peak plasma concentration of **zolpidem** were significantly decreased by 27% and 58%, respectively. The pharmacodynamic effects of **zolpidem**, determined by objective tests and subjective analysis, were significantly attenuated by **rifampin** [107].

3.5.1.BD] **Ritonavir**

- 1) Interaction Effect: an increased risk of extreme sedation and **respiratory depression**
- 2) Summary: According to the manufacturer, coadministered **ritonavir** may increase serum concentrations of **zolpidem**, causing a potential risk of extreme sedation and **respiratory depression** [76]. However, the researchers in one study found that **ritonavir** produced clinically insignificant reductions in the clearance of **zolpidem** [77].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: theoretical
- 6) Clinical Management: Monitor patients for signs and symptoms of **zolpidem** toxicity (sedation, confusion, **respiratory depression**). Reduce doses of **zolpidem** as required.
- 7) Probable Mechanism: increased **zolpidem** serum concentrations due to decreased **zolpidem** metabolism
- 8) Literature Reports

a) A study involving six healthy male volunteers demonstrated that coadministration of **ritonavir** and **zolpidem** did not alter pharmacodynamic effects of **zolpidem**. Each patient received **zolpidem** 5mg and four scheduled doses of **ritonavir** 200mg. The results included reduced **zolpidem** clearance to 78% of control values (p less than 0.08). The elimination half-life was prolonged from 2 to 2.4 hours, which is not statistically significant [75].

3.5.1.BE] **Secobarbital**

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.BF] **Sertraline**

- 1) Interaction Effect: an increased risk of hallucinations
- 2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [105].
- 3) Severity: moderate
- 4) Onset: delayed
- 5) Substantiation: probable
- 6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin-reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [104].

3.5.1.BG] St John's Wort

- 1) Interaction Effect: decreased plasma concentrations of [zolpidem](#)
- 2) Summary: The Cmax and AUC of [zolpidem](#) in 14 healthy male subjects were reduced by approximately 30% with concomitant use of St. John's wort, a CYP3A4 inducer, and [zolpidem](#), a CYP3A4 substrate [69].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of St. John's wort, a CYP3A4 inducer, and [zolpidem](#), a CYP3A4 substrate, may result in decreased [zolpidem](#) plasma concentrations [69].
- 7) Probable Mechanism: induction of CYP3A4-mediated [zolpidem](#) metabolism by St. John's wort
- 8) Literature Reports

a) Concomitant administration of St. John's wort and [zolpidem](#) resulted in decreases in [zolpidem](#) AUC and Cmax and an increase in [zolpidem](#) clearance in 14 healthy male volunteers. The volunteers received one dose of [zolpidem](#) 10 mg on study day 1 (control data), followed by St. John's wort 300 mg 3 times daily on study days 2 to 16; another single dose of [zolpidem](#) 10 mg was given on study day 15. The [zolpidem](#) AUC (mean +/- SD) decreased from 380.3 nanograms (ng) x hr/mL +/- 181.4 ng x hr/mL with the first dose to 265.4 ng x hr/mL +/- 134.2 ng x hr/mL when given concomitantly with St. John's wort, and the Cmax (mean +/- SD) decreased from 83.1 ng/mL +/- 30.1 ng/mL to 55.1 ng/mL +/- 24.8 ng/mL. Clearance (mean +/- SD) increased from 38.4 mL/min +/- 31.5 mL/min to 56.9 mL/min +/- 57.2 mL/min [69].

3.5.1.BH] 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 [83].

- 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 [83].
- 7) Probable Mechanism: additive effects

3.5.1.BI] Telaprevir

- 1) Interaction Effect: decreased [zolpidem](#) plasma concentrations
- 2) Summary: Coadministration of telaprevir and [zolpidem](#) lead to significantly decreased [zolpidem](#) plasma concentrations in a [pharmacokinetic study](#) (n=19). If coadministration of telaprevir and [zolpidem](#) is necessary, titrate the [zolpidem](#) dose based on clinical monitoring [63].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: established
- 6) Clinical Management: Concomitant use of telaprevir and [zolpidem](#) may lead to decreased [zolpidem](#) plasma concentrations. If coadministration of telaprevir and [zolpidem](#) is necessary, monitor patients for decreased [zolpidem](#) efficacy and titrate the [zolpidem](#) dose accordingly. Any dosage adjustments of [zolpidem](#) made during concomitant telaprevir therapy should be re-adjusted following completion of telaprevir therapy [63].
- 7) Probable Mechanism: unknown
- 8) Literature Reports

a) In a [pharmacokinetic study](#) (n=19), concomitant administration of single-dose [zolpidem](#) 5 mg and telaprevir 750 mg every 8 hours for 10 days resulted in significant decreases in [zolpidem](#) AUC and Cmax. The ratio estimate for [zolpidem](#) AUC and Cmax (with telaprevir to without telaprevir) was 0.53 (90% confidence interval (CI), 0.45 to 0.64) and 0.58 (90% CI, 0.52 to 0.66), respectively [63].

3.5.1.BJ] Temazepam

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.1.BK] Thioridazine

- 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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.BL| [Triazolam](#)

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 [103].

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 [103].

7) Probable Mechanism: additive effects

3.5.1.BM| [Venlafaxine](#)

1) Interaction Effect: an increased risk of hallucinations

2) Summary: The publication of five case reports from the Washington Poison Center elucidates potential interactions between [zolpidem](#) and various antidepressant medications. Five patients reported hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. The hallucination episodes all lasted longer than one hour, but resolved without further [sequelae](#) [65].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Observe patients for hallucinatory activity. Alternative anti-insomnia medication may be warranted.

7) Probable Mechanism: unknown

8) Literature Reports

a) The Washington Poison Center reports that they received five different calls from patients experiencing hallucinations after concurrent use of [zolpidem](#) and antidepressant medication. Four of the five reports came from patients taking serotonin-reuptake inhibitors in addition to [zolpidem](#). The antidepressant medications being taken were [desipramine](#), [fluoxetine](#), [sertraline](#), [venlafaxine](#), and [bupropion](#). In each case, the hallucinatory activity lasted longer than one hour, but the patients' symptoms resolved without further [sequelae](#). The authors concluded that the mechanism by which [zolpidem](#) might cause hallucinations has not been firmly established [64].

3.5.1.BN] [Zaleplon](#)

- 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 [103].
- 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 [103].
- 7) Probable Mechanism: additive effects

3.5.2] Drug-Food Combinations**3.5.2.A] [Ethanol](#)**

- 1) Interaction Effect: increased sedation
- 2) Summary: An additive effect on psychomotor performance has been demonstrated when [zolpidem](#) and ethanol are coadministered [109].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Patients should be instructed to avoid ethanol ingestion while taking [zolpidem](#).
- 7) Probable Mechanism: additive CNS depression

3.5.2.B] [Food](#)

- 1) Interaction Effect: decreased [zolpidem](#) plasma concentrations
- 2) Summary: Administration with food resulted in a [zolpidem](#) mean T_{max} prolongation of 60% (from 1.4 to 2.2 hr) and mean AUC and C_{max} reductions of 15% and 25%, respectively, during a clinical study including 30 healthy male subjects receiving [zolpidem](#) 10 mg either while fasting or 20 minutes following a meal. The half-life of [zolpidem](#) was unchanged [103].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: established
- 6) Clinical Management: [Zolpidem](#) should not be administered with or immediately after a meal [103].
- 7) Probable Mechanism: unknown

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) Zolpidem Tartrate

1) Therapeutic

a) Physical Findings

1) Improvement in signs and symptoms of insomnia is indicative of efficacy. Reevaluate if insomnia symptoms persist after 7 to 10 days of treatment [1] [34] [33] [114] [13].

2) Toxic

a) Physical Findings

1) Assess for worsening of depression, suicidality, or new or unusual changes in behavior [1] [34] [33] [114] [13].

4.2] Patient Instructions

A) Zolpidem (By mouth)

Zolpidem Tartrate

Treats insomnia.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an allergic reaction to zolpidem.

How to Use This Medicine:

Tablet, Long Acting Tablet

Take your medicine as directed.

This medicine is not for long-term use.

This medicine is usually taken just before bedtime, or when you are having trouble falling asleep. You should not take this medicine if you are not able to sleep or rest for 7 to 8 hours before you need to be active again.

This medicine should not be taken with food or right after a meal.

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

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

Use this medicine only when you cannot sleep. You do not need to keep a schedule for taking it.

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

Drugs and Foods to Avoid:

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

Some medicines and foods can affect how zolpidem works. Tell your doctor if you are taking ketoconazole, rifampin, or depression 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:

Tell your doctor if you are pregnant or breastfeeding, or if you have kidney, liver, or lung disease, [myasthenia gravis](#), or breathing problems, including [sleep apnea](#). Tell your doctor if you have ever been addicted to alcohol or drugs, or if you have a history of depression or mental illness.

Tell your doctor if you develop any unusual thoughts or behaviors. This includes aggressive behavior, confusion, hallucinations (seeing, hearing, or feeling things that are not there), anxiety, depression, or thoughts of hurting yourself.

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

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

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. If you take this medicine every night, you might have side effects for a few days when you stop using it. This includes nausea, vomiting, crying, and trouble sleeping.

Call your doctor if you still have trouble sleeping after you take this medicine for 7 to 10 days.

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

Possible Side Effects While Using This Medicine:

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

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

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

Memory loss

Seeing, hearing, or feeling things that are not there

Severe confusion, drowsiness, muscle weakness

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

Daytime drowsiness

Diarrhea, nausea

Headache, lightheadedness, or dizziness

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

B) Zolpidem (Into the mouth)

[Zolpidem](#)

Treats insomnia (trouble sleeping).

When This Medicine Should Not Be Used:

Do not use this medicine if you have had an [allergic reaction](#) to [zolpidem](#).

How to Use This Medicine:

Spray, Tablet

Take your medicine as directed.

This medicine is not for long-term use.

This medicine is usually taken just before bedtime, or when you are having trouble falling asleep. You should not use this medicine if you are not able to sleep or rest for about 7 to 8 hours before you need to be active again. Do not take the Intermezzo® brand of medicine unless you have at least 4 hours to sleep or rest.

This medicine should not be taken with food or right after a meal. It is best to take this medicine on an empty stomach.

Oral spray:

If you are using the oral spray for the first time, it must be primed by spraying it for 5 times in a safe direction away from your face and other people. If the oral spray has not been used for 14 days, it must be primed again with 1 spray.

To use: First, pull the child-resistant cap to separate it from the base. Remove the clear protective cap from the pump. Hold the container upright with the black spray opening pointed directly into your mouth. Fully press down on the pump to make sure that a full dose (5 mg) of this medicine is sprayed directly into the mouth over the tongue. If a 10 mg dose is prescribed by your doctor, a second spray should be given. Put the clear protective cap back over the pump after each use.

Sublingual tablet:

Do not use a tablet that is broken.

Do not open the blister pack that contains the tablet until you are ready to take your medicine. Do not use the tablet if the seal of the blister pack is broken.

Remove the tablet from the blister pack by [peeling](#) back the top layer of paper, then push the tablet through the foil.

Place the tablet under your tongue. Let it dissolve completely in your mouth. Do not swallow the tablet whole. Do not take with water.

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

Use this medicine only when you cannot sleep. You do not need to keep a schedule for taking it.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Store the oral spray in an upright position.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed. Throw away the child-resistant container of the oral spray when the 60 sprays have been used.

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

Drugs and Foods to Avoid:

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

Make sure your doctor knows if you also use [ketoconazole](#) (Nizoral®), [rifampin](#) (Rifadin®, Rimactane®), or medicine to treat depression (such as [imipramine](#), Tofranil®, [sertraline](#), Zoloft®).

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. Using these together with [zolpidem](#) may increase the risk of side effects.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have [kidney disease](#), liver disease, [myasthenia gravis](#), lung disease, or breathing problems, including [sleep apnea](#). Tell your doctor if you have ever been addicted to alcohol or other drugs (including street drugs), or if you have a history of depression or mental illness.

Tell your doctor if you develop any unusual thoughts or behaviors. This includes aggressive behavior, confusion, hallucinations (seeing, hearing, or feeling things that are not there), anxiety, depression, or thoughts of hurting yourself.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous until you know how this medicine affects you. Be especially careful in the morning after you take a dose, because the medicine could still be working and making you less alert.

This medicine may cause you to do things while you are still asleep that you may not remember the next morning. It is possible you could drive a car, sleepwalk, have sex, make phone calls, or prepare and eat food while you are asleep or not fully awake. Tell your doctor right away if you learn that this has happened.

For some people, this medicine stays in the body longer than it does for other people. This means that you might still feel sleepy and less alert the next morning, because the medicine is still working. Tell your doctor if this happens. Women are more likely to have this problem than men are, so women should get a lower starting dose than men do.

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. If you take this medicine every night, you might have side effects for a few days when you stop using it. This includes nausea, vomiting, crying, and trouble sleeping.

Call your doctor if you still have trouble sleeping after using this medicine for 7 to 10 days.

Possible Side Effects While Using This Medicine:

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

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

Anxiety, agitation, depression, nervousness, unusual behavior, thoughts of hurting yourself

Seeing, hearing, or feeling things that are not there

Severe confusion, drowsiness, muscle weakness

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

Daytime drowsiness

Diarrhea, nausea

Hangover feeling

Headache, lightheadedness, or dizziness

Memory loss

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

4.3] Place In Therapy

A) Insomnia

1) **Zolpidem** oral spray, immediate-release tablets, and sublingual tablets (Edluar(TM)) are indicated for the short-term treatment of insomnia characterized by **sleep initiation difficulties** [34] [13] [103]. The extended-release tablet is indicated for the treatment of insomnia, characterized by difficulties of sleep onset and/or sleep maintenance [140]. Low-dose sublingual **zolpidem** tartrate (Intermezzo(R)) is indicated for as needed use in the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep, provided 4 hours of bedtime remain before the planned time of waking [1].

B) Summary

1) The primary therapeutic use of **zolpidem** is the short-term management of insomnia [141] [142]. **Zolpidem** may represent a significant therapeutic advantage over benzodiazepines for some patients due to its lower incidence of adverse effects such as daytime sedation, amnesia, tolerance, dependence, and rebound insomnia upon withdrawal after therapeutic doses [143] [144] [145] [146] [142].

2) In a driving study, healthy subjects who received low-dose sublingual **zolpidem** tartrate (Intermezzo(R)) with fewer than four hours of bedtime remaining had evidence of impaired driving compared to subjects who received placebo. The risk of next-day driving impairment (and **psychomotor impairment**) is increased

if low-dose sublingual [zolpidem](#) tartrate (Intermezzo(R)) is taken with less than 4 hours of bedtime remaining, if higher than recommended dose is taken, if co-administered with other CNS depressants, or co-administered with other drugs that increase the blood levels of [zolpidem](#) [1].

3) [Zolpidem](#) produces a quality and pattern of sleep very similar to that of normal physiological sleep, and may produce less adverse effects related to derangement of normal sleep [147] [145]; whereas benzodiazepines induce alterations in normal EEG and sleep patterns both during hypnotic therapy (eg, suppression of REM sleep) and upon hypnotic withdrawal (eg, REM rebound) [148] [149] [150] [145].

4) Despite promotion of [zolpidem](#) as having a favorable safety profile, use of [zolpidem](#) was associated with a near doubling of risk of [hip fracture](#) in elderly patients (mean age 82 years) in a large case-control study (1222 cases, 4888 controls). Benzodiazepines, antipsychotic medications, and antidepressants also were associated with increased risk of [hip fracture](#) in the elderly, but no risk was higher than that with [zolpidem](#) [151].

5) The pharmacokinetic profile of [zolpidem](#) is quite favorable for a hypnotic [141]. Slowly absorbed and/or excreted drugs such as loperidol or [flurazepam](#) may cause drug hangover and impaired daytime performance. [Zolpidem](#) reaches peak plasma concentrations approximately one hour after oral ingestion, and has an elimination half-life of approximately 2.5 to 5 hours, which may reduce the incidence of these adverse effects [141].

4.4] Mechanism of Action / Pharmacology

A) [Zolpidem](#) Tartrate

1) Mechanism Of Action

a) [Zolpidem](#) is an imidazopyridine sedative-hypnotic that is structurally unrelated to the barbiturates and benzodiazepines [121] [124]. It has a rapid onset and short duration of action, and is said to have a more favorable adverse effect profile than the benzodiazepines [125] [126], and preliminary animal data suggest that tolerance may not develop to the drug [127]. Thus, [zolpidem](#) may have less abuse potential than the benzodiazepines.

b) Pharmacologically, [zolpidem](#) binds to the omega-1 subclass of benzodiazepine receptors in the brain [128] [126] without binding to peripheral benzodiazepine receptors [129] [130]. This has been corroborated by the observation that [zolpidem](#) has little or no muscle relaxant properties [131].

c) [Zolpidem](#) has been shown to reduce sleep latency (time to fall asleep) [126] [132] [133], decrease the number of awakenings [134], and to increase total sleep time [124]. While REM sleep is not significantly decreased, the onset of REM is delayed [135] [124]. The REM/non-REM ratio is not significantly altered [135]. Slow wave (stages 3 and 4) sleep time is increased [135]. This more closely resembles natural sleep than does [hypnosis](#) induced by the benzodiazepines; this may result in fewer adverse reactions related to disturbance of normal sleep patterns [126].

d) [Zolpidem](#) does not modify the structure of uninterrupted sleep but significantly reduces the Cyclic Alternating Pattern (CAP) Rate (the percentage of CAP during sleep) which increased due to white noise (45-55 dB (A)). CAP is a physiological EEG component of non-REM sleep that reflects a condition of sustained arousal instability, and, subsequently, the subjective appreciation of sleep quality. CAP Rate to total non-REM sleep of 25% to 45% is reported as satisfactory sleep, 45% to 60% refers to moderate sleep disturbances, and above 60% as severe insomnia [136] [137] [138].

4.5] Therapeutic Uses

4.5.A] **Zolpidem Tartrate**

4.5.A.1] **Dystonia**

a) 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](#)

b) Summary:

Reduced **dystonia** in 3 patients with LUBAG or X-linked dystonia-parkinsonism syndrome [3]

c) Adult:

1) Three patients with a rare dystonia-parkinsonism syndrome (X- linked) experienced some relief with **zolpidem** treatment. All 3 men (age range 36 to 41 years) manifested torticollis, body and limb bradykinesia, and rigidity. Scores on the Burke-Fahn-Marsden (BFM) **dystonia** scale ranged from 30 to 66, and motor United Parkinson Disease Rating Scale scores ranged from 36.5 to 54.5 before treatment. Oral **zolpidem** 10 mg brought 31% to 100% improvement in **dystonia** within 1 to 2 hours (onset of effect, 15 to 45 minutes). Duration of action initially ranged from 2.5 to 8 hours and was reduced to 2 to 3 hours with chronic use. One man adapted, with the use of **caffeine**, to **zolpidem** 10 mg every 2 hours, with efficacy maintained at 1 year. Another man, at a dose of 10 mg twice daily, developed diarrhea after 6 months, which stopped on discontinuation of **zolpidem**. The third man, for whom a dose lasted 2 hours, could not afford the medication and ran out of donated tablets after 2 months [3].

4.5.A.2] **Insomnia, Characterized by difficulty returning to sleep after middle-of-the-night awakening**

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (SL tablet (Intermezzo(R))); **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](#)

b) Summary:

Zolpidem tartrate SL tablet is indicated for use as needed for treating insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep; it is not indicated when the patient has fewer than 4 hours of bedtime remaining prior to the planned time of waking [1].

c) Adult:

1) Clinical Trials

a) Efficacy of [zolpidem](#) tartrate SL tablets in adults with insomnia, characterized by difficulty returning to sleep following a middle-of-the-night awakening, was established in 2 randomized, double-blind, placebo-controlled studies (Studies 1 and 2). Eligible patients met the criteria for [primary insomnia](#) (DSM-IV-TR) and experienced at least 3 prolonged middle-of-the-night awakening per week that lasted at least 30 minutes in duration [1]. Study 1 was a 3-period, crossover sleep laboratory study. Adults (n=82; 58 females; mean age 45.9 years) enrolled in the study received randomized treatments of [zolpidem](#) tartrate SL tablet doses of 3.5 mg or 1.75 mg and placebo; all 3 treatments were administered in a double-blind fashion, separated by a 5 to 12 day washout interval. Compared with placebo, the decreases in latency to persistent sleep (LPS) measured on [polysomnography](#) (primary endpoint) were significant for both doses (1.75 mg, 28.12 minutes (min) vs 16.89 min (p less than 0.001); 3.5 mg, 28.12 min vs 9.69 min (p less than 0.001)) following a scheduled middle-of-the-night awakening. Both doses significantly decreased patient estimate of sleep latency compared with placebo (40.43 min vs 28.58 min, and 40.40 min vs 25.23 min, respectively; p less than 0.001) following a scheduled middle-of-the-night awakening. Between dose difference was significant for the objective measure of sleep latency, favoring the 3.5 mg dose (p less than 0.001); however, no between dose difference was seen on the subjective measure. No serious adverse effects were reported in any treatment group [2]. Study 2 was a 4-week, outpatient study where adults (n=295; 201 females; median age, 43 years) were randomized to receive either 3.5 mg of SL [zolpidem](#) tartrate or placebo on an as-needed basis. The study drug was only taken when patients had difficulty returning to sleep after waking up in the middle-of-the-night; the drug was taken only if patients had at least 4 hours of remaining bed time. Compared with placebo, patient-estimated time to fall back to sleep was significantly shorter in this study. Adverse effects that occurred more often in patients receiving SL [zolpidem](#) tartrate compared with placebo included [gastrointestinal disorders](#) (4% vs 2%), headache (3% vs 1%), and fatigue (1% vs 0%) [1].

2) Driving Safety

a) The effect of middle-of-the-night administration of [zolpidem](#) tartrate SL tablets on next-morning driving performance was evaluated in a randomized, double-blind, placebo- and active-controlled, 4-period, crossover study. Healthy adults (n=40) enrolled in the study received the 4 randomized treatments of [zolpidem](#) tartrate 3.5 mg SL tablet 4 hours before driving, [zolpidem](#) tartrate 3.5 mg SL tablet 3 hours before driving, placebo, and a positive control (an unapproved sedative-hypnotic) given nine hours before driving. The primary outcome measure was the change in the standard deviation of lateral position (SDLP), a measure of driving impairment. The results were analyzed using a symmetry analysis, which determined the proportion of subjects whose change from their own SDLP in the placebo condition was statistically significantly above a threshold thought to reflect clinically meaningful driving impairment. The symmetry analysis showed a statistically significant impairing effect when driving began 3 hours after administration of [zolpidem](#) tartrate 3.5 mg SL tablet; driving was terminated for one subject (female, 23 years old) due to somnolence. When driving began 4 hours after administration of [zolpidem](#) tartrate 3.5 mg SL tablet, statistically significant impairment was not found; although, [zolpidem](#) tartrate 3.5 mg SL tablet was numerically worse than placebo. [Zolpidem](#) blood levels were not measured in this study. A negative effect on SDLP may remain in some patients 4

hours after the 1.75 mg dose in women, and after the 3.5 mg dose in men, such that a potential negative effect on driving cannot be completely excluded [1].

4.5.A.3] Insomnia, Long-term treatment

a) 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](#)

b) Summary:

Immediate-release [zolpidem](#) was demonstrated as safe and effective for the long-term treatment (up to 360 days) of insomnia [4], with little evidence of tolerance or rebound insomnia reported [5]. Extended-release [zolpidem](#) was effective for the long-term treatment of chronic [primary insomnia](#) based on patient self-reports, in a 26-week, phase 3, double-blind, randomized, placebo-controlled trial (n=1018) [6].

c) Adult:

1) Immediate-Release Tablets

a) An open, single-blind trial was conducted in 14 elderly psychiatric patients suffering from severe insomnia who received [zolpidem](#) 20 mg nightly for 179 days [7]. Polysomnographic recordings were performed prior to the initiation of the study, and on days 30, 90, and 179. Improvements in total sleep time, sleep efficiency, and percentage of REM sleep were observed after 30 days and maintained at 179 days. Mild adverse effects that were noted in a few patients included unsteadiness, faintness, giddiness, unclear speech, headache, nausea, and vertigo.

b) [Zolpidem](#) is safe and effective for long-term treatment and a 15-mg dose offers no clinical benefit over a 10-mg dose. [Zolpidem](#) was studied in a randomized, double-blind, placebo-controlled multicenter trial in the treatment of [chronic insomnia](#) for a period of 35 nights [8]. Seventy-five patients were randomized to one of 3 treatment groups: [zolpidem](#) 10 mg, [zolpidem](#) 15 mg, or placebo. The beneficial effects on latency to persistent sleep and sleep efficiency were observed within the first week of treatment with both [zolpidem](#) regimens and were maintained throughout the trial, indicating no development of tolerance. The 15-mg group experienced worse sleep quality and greater wake time on the first posttreatment night; however, no discontinuation effects were noted during the 2 subsequent nights posttreatment.

c) Further data demonstrated the effectiveness of [zolpidem](#) in the treatment of insomnia in a group of 155 patients for a period of 12 weeks [9]. Patients were initiated on [zolpidem](#) 15 mg; 33 patients had their dose reduced to 10 mg during the study period because of an adverse effect. Tolerance was not observed throughout the study period and rebound insomnia was not reported, despite the use of a higher than recommended dose of [zolpidem](#). The incidence of side effects was higher in the group receiving the 15-mg

dosage; however, most side effects were mild and primarily involved drowsiness, fatigue and headache.

d) A long-term, multicenter, open trial was conducted in which 96 insomniacs (ages 22 to 86) received [zolpidem](#) 10 to 20 mg nightly for a period of 180 to 360 nights. Sixty-nine patients (72%) completed the initial 180 nights of therapy; 49 patients continued therapy for a total of 360 nights. Decreased onset of sleep latency, number of nocturnal awakenings, duration of sleep and quality of sleep was improved from baseline in 90% of patients. Rebound and withdrawal effects were not observed. Side effects occurred in 7.8% of patients and included feelings of strangeness, drowsiness, amnesia, nausea and confusion [4].

e) [Zolpidem](#) was studied in 107 outpatients with insomnia over a 6-month period in a single-blind, flexible dose trial. Improvements were noted both by the patients and the treating physicians in all efficacy measures including time to fall asleep, total amount of sleep, and number of awakenings; improvement persisted throughout the 6-month trial. Tolerance did not develop during the study period and there was no evidence of rebound insomnia. The authors concluded that 10 mg nightly was an appropriate initial dose but that adjustment to 20 mg was safe for most patients for whom the lower dose was ineffective [5].

2) Extended-Release Tablets

a) Extended-release [zolpidem](#) effectively treated chronic [primary insomnia](#) based on patient self-reports, in a 26-week, phase 3b, multicenter, double-blind, randomized, placebo-controlled trial. Patients (n=1018; mean age, 45.7 +/- 11 years), with chronic [primary insomnia](#) were enrolled if they reported at least 1 hour of wakefulness for at least 4 nights a week during the preceding month, and spent 6.5 to 8.5 hours in bed each night trying to sleep during the 2 preceding weeks. After a baseline, 7-day (+/- 3 days) run-in period, patients with a mean total sleep time (TST) of at least 3 hours (hr) and a mean wake time after sleep onset (WASO) of at least 40 minutes (min), were randomized to receive [zolpidem](#) 12.5 mg extended-release tablets (n=669) or placebo (n=349) nightly for 24 weeks, followed by a run-out period of no medication for 7 days (+/- 3 days). All patients received sleep hygiene instructions. The primary endpoint was the score on the Patient's Global Impression (PGI), item 1 (treatment aid to sleep) at week 12, assessed by the patient and scored as "helped me sleep" (1), "did not affect my sleep" (2), or "worsened my sleep" (3). A significant improvement (p less than 0.0001) was seen in the primary endpoint in the [zolpidem](#) group compared with the placebo group, with 89.8% of patients in the [zolpidem](#) group and 51.4% of patients in the placebo group reporting that the study drug helped them sleep. Treatment benefit was significantly improved in the [zolpidem](#) group compared with the placebo group on all 4 items of the PGI (p less than 0.0001 for each measurement) and the Clinical Global Impression - Improvement (CGI-I) scale (p less than 0.0001) at each 4-week interval for the entire 24-week treatment period. Significant improvements in the [zolpidem](#) group compared with the placebo group also occurred in TST (p less than 0.0001), WASO (p less than 0.0001), duration of sleep onset latency (SOL) (p less than or equal to 0.0014), ability to concentrate in the morning (p less than 0.001 for months 1 to 5; p=0.0014 for month 6), and level of sleepiness in the morning (p less than 0.0001), each self-reported on the Patient's Morning Questionnaire (PMQ). Quality of sleep (QOS) and number of awakenings (NAW), also part of the PMQ, were significantly improved in the [zolpidem](#) group compared with the placebo group for

months 2 to 6 (p less than 0.0001), but not for month 1 (p=0.0515). The 8-item Epworth Sleepiness Scale (ESS), also completed by the patient, was significantly improved in the [zolpidem](#) group compared with the placebo group at all time points except months 1 and 6. TST (p less than 0.0001) and WASO (p less than 0.001) scores were significantly better in the placebo group on night 1 after discontinuation of study drug but no differences were observed between groups on nights 2 and 3. No serious treatment-related adverse events were reported [6].

4.5.A.4] Insomnia, Short-term treatment

FDA Labeled Indication

a) Overview

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

Efficacy: Adult, Effective; Pediatric, Ineffective

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

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

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

b) Summary:

The SL tablets of [zolpidem](#) tartrate are indicated for the short-term treatment of insomnia characterized by difficulties of sleep onset [15].

The immediate-release tablets and oral spray formulations of [zolpidem](#) tartrate are indicated in the short-term treatment of insomnia [11] [13].

The extended-release tablets of [zolpidem](#) tartrate are indicated for the treatment of insomnia, characterized by difficulties of sleep onset, sleep maintenance, or both [12].

Extended-release [zolpidem](#), at a nightly dose of 6.25 mg, effectively improved wake time after sleep onset in elderly patients with [primary insomnia](#) in a 3-week, multicenter, double-blind, randomized, placebo-controlled trial (n=205) [16].

In an 8-week, placebo-controlled study, oral, immediate-release [zolpidem](#) was not effective in treating insomnia associated with ADHD in pediatric patients aged 6 to 17 years [11].

c) Adult:

1) Sublingual Tablets

a) The efficacy of SL tablets for the short-term treatment of insomnia characterized by [sleep initiation difficulties](#) is based on its equal bioequivalence to immediate-release oral tablets [15].

2) Oral Spray

a) The efficacy of the oral spray for the short-term treatment of insomnia characterized by [sleep initiation difficulties](#) is based on its equal bioequivalence to immediate-release oral tablets [13].

3) Immediate-Release Tablets

a) **Zolpidem** used intermittently was as effective as nightly administration. **Zolpidem** 10 mg was administered to 154 chronic insomniacs for 2 weeks via a blister pack that contained either all **zolpidem** tablets (continuous treatment) or 5 **zolpidem** tablets plus 2 placebo for each week (intermittent treatment). In the intermittent treatment group, subjective total sleep time increased from 5.7 hours (at baseline) to 6.9 hours (for the second week of treatment). In the continuous treatment group, subjective total sleep time increased from 6.1 hours at baseline to 7 hours for the second week. There was no statistical difference between the 2 groups [17].

b) In a placebo-controlled, double-blind, crossover study, **zolpidem** reduced nighttime awakening and improved daytime energy in patients with **fibromyalgia**, but had no effect on pain symptoms. Over a total of 16 days and nights, 19 patients were randomized to receive bedtime doses of either placebo or **zolpidem** (5, 10, or 15 mg) for 4 nights and then crossed over every fourth night (with no washout period) to each other treatment. In comparison with placebo, **zolpidem** 10 and 15 mg were both associated with sleep improvement and significantly fewer nocturnal awakenings; **zolpidem** 5 and 10 mg produced significantly longer total sleep times; and **zolpidem** 15 mg induced sleep the most rapidly. Daytime assessments revealed no effects on energy or wakefulness, but evening sluggishness was more profound with **zolpidem** 5 and 10 mg ($p=0.027$). **Fibromyalgia** pain symptoms and severity were not altered by treatment [18].

c) A total of 1152 patients (ages 18 to 95 years) with insomnia were evaluated in a multicenter trial assessing the safety and efficacy of **zolpidem**. **Zolpidem** provided benefit in terms of improvement in measured sleep parameters, the quality of sleep, and the patients' opinion of their condition on waking. After the third night of receiving **zolpidem** 10 mg nightly, 21.5% of patients required an increase in **zolpidem** dosage to 20 mg. The mean duration of treatment was 11.5 days; the drug was well tolerated at both doses. Only 4.3% of patients reported adverse effects; however, there were slightly more adverse effects reported for the 20-mg dose than the 10-mg dose (5.3% vs 3.7%, respectively). The most frequent adverse effects were daytime sedation, drowsiness, headache, and asthenia [19].

d) **Zolpidem** 10 and 20 mg were compared with placebo in a double-blind study in patients with insomnia ($n=88$). Patients received no treatment for 3 nights as a control period, then **zolpidem** 10 or 20 mg or placebo at bedtime for 3 weeks followed by a control period of 7 days. With the exception of dreaming, which was slightly reduced, all parameters measured were improved with either dose of **zolpidem** over placebo. Time to fall asleep and the number of night time awakenings were significantly reduced and the quality and duration of sleep were significantly improved over placebo. There was no evidence of daytime sedation, dependence, or rebound insomnia with **zolpidem** as compared with placebo [20].

e) In a double-blind study, patients with insomnia ($n=60$) were randomized to receive **zolpidem** 10 or 20 mg at bedtime for 7 days with 2 days of placebo run-in before, and 3 days of placebo withdrawal after, active drug administration. Sleep latency was significantly shorter with **zolpidem** than with placebo, and sleep duration was significantly longer. Nocturnal awakenings also were reduced with **zolpidem**. Quality of sleep was improved over placebo. Tolerance, rebound insomnia, or daytime interference with cognitive or psychomotor functioning were not observed. The authors judged **zolpidem** 10 mg as effective as 20 mg, and recommended 10 mg as the preferred dosage for insomnia [21].

f) The effects of single 10-, 20-, and 30-mg doses of **zolpidem** on sleep structure and residual daytime impairment were studied in 12 subjects. Subjects were randomized to receive **diazepam** 10 mg, **zolpidem** 10, 20, or 30 mg, or placebo over 6 nights such that placebo was administered twice during the study period. **Zolpidem** markedly increased slow-wave sleep (stages 3 and 4) and reduced stage 2 sleep. Although the duration of REM sleep was unchanged, it was delayed. Stage 1 sleep also was unchanged. Sleep latency was decreased with **zolpidem**, and sleep time and quality were increased. No residual effects were reported with **zolpidem**, and daytime performance was not impaired [22].

g) Abrupt shift to **zolpidem** treatment for insomnia was effective in a multicenter study of 299 patients with insomnia resistant to or not tolerant of prior benzodiazepine treatment (**triazolam** 0.125 to 0.25 mg, **lorazepam** 1 mg, **lormetazepam** 1 mg). **Zolpidem** 10 to 20 mg at bedtime for 7 days significantly improved all sleep parameters (sleep latency, total sleep time, and number of nocturnal awakenings) and the Saint Mary Hospital Sleep Questionnaire scores (p less than 0.001). Of 274 evaluable patients, 229 (83.5%) did not exhibit benzodiazepine withdrawal symptoms; in 17 (6.2%), switch to **zolpidem** was considered unsuccessful [23].

4) Extended-Release Tablets

a) Clinical Studies

1) In a double-blind, randomized, parallel-group, 3-week trial involving 212 adult outpatients, 18 to 64 years of age, who were given either **zolpidem tartrate** 12.5 mg extended-release tablets or placebo. Wake time after sleep onset (WASO) and objective measures of sleep induction, such as latency to persistent sleep (LPS), were used to compare efficacy. **Zolpidem** decreased WASO for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Polysomnography readings indicated the **zolpidem** was superior to placebo in decreasing LPS during the first 2 nights of treatment and following 2 weeks of treatment. In addition, patients on **zolpidem** reported a better global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment compared with patients on placebo [12].

2) Extended-release **zolpidem**, at a dose of 6.25 mg, was safe and effective for the short-term treatment of primary insomnia in elderly patients in a multicenter, double-blind, randomized, placebo-controlled trial. Patients ($n=205$), 65 to 87 years of age (mean age, 70.2 \pm 4.5 years), with primary insomnia, were enrolled if they reported at least 1 hour of wakefulness after sleep onset for at least 3 nights a week during the preceding month, and spent 6.5 to 9 hours in bed each night during the 2 preceding weeks. After a baseline period of single-blind placebo for 2 nights in a sleep laboratory, patients with wake time after sleep onset (WASO) of at least 30 minutes (min) on each night with a mean WASO of 40 min, and a total sleep time (TST) of 3 to 7 hours on each night, were randomized to receive **zolpidem** 6.25 mg extended-release tablets ($n=99$) or placebo ($n=106$) nightly for 3 weeks, followed by a discontinuation placebo phase for 2 nights. At baseline, the 1- to 6-hour (hr) WASO was 67 min, 16 seconds (sec) \pm 33 min, 41 sec for the **zolpidem** group and 70 min, 15 sec \pm 33 min, 37 sec for the placebo group ($p=0.53$), while the number of awakenings was significantly lower for the **zolpidem** group (10.8 \pm 3.4) compared with the placebo group (12.1 \pm 4.1 ($p=0.02$)). In

addition, quality of sleep (rated by patients on a Lickert scale from 1=excellent to 4=poor) was significantly better in the zolpidem group (2.8 +/- 0.6) at baseline compared with the placebo group (3 +/- 0.7; $p=0.009$). Polysomnography (PSG) readings were averaged on nights 1 and 2, and on nights 15 and 16. Zolpidem significantly reduced the adjusted mean 1- to 6-hr WASO, the primary endpoint, by 32 min, 41 sec compared with 6 min, 59 sec in the placebo group at nights 1 and 2 (adjusted mean difference, 25 min, 42 sec; 95% CI, 19 min, 5 sec to 32 min, 19 sec; p less than 0.0001) and by 18 min, 22 sec compared with 6 min, 56 sec in the placebo group at nights 15 and 16 (adjusted mean difference, 11 min, 27 sec; 95% CI, 3 min, 39 sec to 19 min, 14 sec; $p=0.0042$). Sleep efficiency was significantly improved in the zolpidem group at nights 1 and 2 compared with placebo (adjusted mean difference, 0.073; 95% CI, 0.052 to 0.093; p less than 0.0001) but not at nights 15 and 16 ($p=0.0509$); while latency to persistent sleep was significantly improved in the zolpidem versus placebo groups at both nights 1 and 2 (adjusted mean difference, 10 min, 15 sec (95% CI, 5 min, 4 sec to 15 min, 25 sec; $p=0.0001$) and nights 15 and 16 (adjusted mean difference, 5 min, 49 sec; 95% CI, 0.43 min to 10.54 min; $p=0.0255$). Patient-reported estimates for total sleep time, WASO, number of awakenings, and refreshing quality of sleep were all significantly improved in the zolpidem group compared with the placebo group at week 1, 2, and 3. Patient-reported sleep latency was only significantly improved in the zolpidem group compared with the placebo group at week 1, but not at weeks 2 or 3, while patient-reported sleep quality was improved at weeks 1 and 2, but not 3. No differences in next-morning residual effects or adverse events were reported between the groups [16].

3j) As-needed use of zolpidem extended-release 12.5 mg tablets on 3 to 7 nights/week, significantly improved patient global impression of aid to sleep and patient-reported specific sleep parameters for sleep induction and sleep maintenance compared with placebo in a 24-week, double-blind, randomized study of adult patients (aged 18 to 64 years) with primary insomnia ($n=1025$). Throughout the 6 months, there was no significant increase in frequency of drug intake [12].

a) Residual Effects

1j) The effects of zolpidem tartrate extended-release tablets on vigilance, memory, or motor function were studied using neurocognitive tests in 5 clinical studies. Three controlled studies were conducted in adults (18 to 64 years of age) who were given zolpidem extended-release 12.5-mg tablets and 2 controlled studies were conducted in the elderly (65 years or older) who were given either the 6.25-mg or 12.5-mg extended-release tablet as a nighttime dose. No significant decrease in performance was noticed after 8 hours and next-day residual effects were absent at both dose strengths. Next-day somnolence was noted by 15% of adult patients on the 12.5-mg dose versus 2% by the placebo group, and among elderly patients, 6% reported next-day somnolence at the 6.25-mg extended-release tablet compared with 5% by the placebo group during the 3-week clinical trials. In the 6-month trial, next-day somnolence occurred in 5.7% of patients

treated with zolpidem extended-release compared with 2% in the placebo group [12].

b) Rebound Insomnia upon Withdrawal

1) Rebound effects, defined as a dose-dependent worsening in sleep parameters compared with baseline following discontinuation, were evaluated in the two 3-week placebo-controlled approval studies in patients with primary insomnia. Rebound insomnia was observed only after the first night of abrupt discontinuation of zolpidem extended-release tablets. In the 6-month, placebo-controlled study of as-needed use of zolpidem extended-release tablets (3 to 7 nights/week), a rebound effect was observed for total sleep time during the first night off medication within the first month of treatment only [12].

d) Pediatric:

1) Oral, immediate-release zolpidem 0.25 mg/kg at bedtime did not decrease sleep latency compared with placebo in pediatric patients aged 6 to 17 years with insomnia associated with ADHD in an 8-week, placebo-controlled study. The most frequent treatment-emergent adverse events were psychiatric and nervous system disorders, with dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations (7.4% vs 0%) occurring at a higher frequency in the zolpidem group than placebo [11].

4.5.A.5] Insomnia - Posttraumatic stress disorder

a) 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

b) Summary:

Effective in case reports for insomnia associated with posttraumatic stress disorder [10]

c) Adult:

1) In 3 case reports zolpidem was beneficial in treating insomnia associated with posttraumatic stress disorder (PTSD). One veteran with PTSD had zolpidem substituted for his trazodone which was causing morning hangover. He gained 2 to 3 hours of sleep per night with the switch. Another veteran received trazodone and doxepin trials for his insomnia which resulted in exacerbation of his restless legs syndrome. Zolpidem was instituted with the patient then getting 6 or more hours sleep per night. A third veteran had insomnia due to oversedation by his nefazodone and risperidone. The zolpidem was substituted for the risperidone and the patient's sleep improved [10].

4.5.A.6] Insomnia - Selective serotonin re-uptake inhibitor adverse reaction**a) Overview**

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

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

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

b) Summary:

Effective in alleviating sleep problems secondary to SSRI use [24]

c) Adult:

1) [Zolpidem](#) successfully improved sleep in patients with SSRI-induced insomnia. Patients with insomnia of at least 2 weeks duration secondary to [sertraline](#), [fluoxetine](#), or [paroxetine](#) were randomized to receive [zolpidem](#) 10 mg (n=94) or placebo (n=96) for 4 weeks. Throughout the study, [zolpidem](#) significantly improved sleep by increasing sleep time (p less than 0.05) and increasing sleep quality (p less than 0.01). During weeks 1, 2, and 4 there was also significantly fewer awakenings seen in the [zolpidem](#) group (p less than 0.05). Similar rates of adverse drug reactions were seen in both groups. Short-term [zolpidem](#) appears to be effective and safe when used with an SSRI for insomnia [24].

4.5.A.7] Neuroleptic-induced Parkinsonism**a) 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](#)

b) Summary:

Reduced tremor in one case of drug-induced [parkinsonism](#) [25]

c) Adult:

1) [Zolpidem](#) reduced the refractory tremors associated with antipsychotic-induced [parkinsonism](#) in a 35-year-old institutionalized man. The severe hand tremors were attributed primarily to antipsychotic treatment, although lead intoxication and [polysubstance abuse](#) may have been contributing factors. The tremors did not improve when antipsychotic treatment was changed to [risperidone](#), [olanzapine](#), or [clozapine](#). The tremors were unresponsive to treatment with [benztropine](#), [biperiden](#), [diphenhydramine](#), [amantadine](#), and [propranolol](#). With [zolpidem](#) 10 mg 4 times daily, his tremor score was reduced from 29 to 9. Three months after the initiation of [zolpidem](#), he decompensated, and his antipsychotic medication was changed to [clozapine](#) 50

mg/day, while [zolpidem](#) was continued. Because of marked sedation, [zolpidem](#) was tapered and discontinued, resulting in an increase in tremor score to 30. [Zolpidem](#) was reintroduced at 5 mg 4 times per day, with a reduction in tremor score to 8. At 2-year follow-up, his tremor remained improved [25].

4.5.A.8] Preoperative sedation

a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

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

b) Summary:

Effective for preoperative sedation [26]

Duration of action may be longer than desirable for most short-stay or outpatient procedures

c) Adult:

1) The efficacy of single oral doses of [zolpidem](#) 10 and 20 mg compared with placebo for preoperative sedation was studied in 37 patients undergoing minor [gynecological surgery](#). [Zolpidem](#) was found to be superior to placebo, producing good preoperative sedation after 10- or 20-mg doses, and [anterograde amnesia](#) after 20-mg doses. In addition, smaller doses of [thiopental](#) were required for [induction of anesthesia](#) in patients receiving [zolpidem](#). However, its duration of action was prolonged enough that the authors deemed it unsatisfactory as a premedication for short procedures (eg, in outpatient or day surgery). Recovery of psychomotor function was prolonged in patients receiving [zolpidem](#), and was delayed from 5 to 9 hours in these patients. The authors concluded that [zolpidem](#) may be an effective preoperative medication in those instances where sedation, [hypnosis](#), and amnesia are desired [26].

4.5.A.9] Restless legs syndrome

a) 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](#)

b) Summary:

Effectively relieved symptoms of [restless legs syndrome](#) in 8 patients [27]

c) Adult:

1j) Treatment with [zolpidem](#) relieved symptoms of [restless legs syndrome](#) in several patients that had failed other therapies. In a prospective, open-label, case series study, patients (n=8; 32 to 75 years of age) with an average 2-year history of [restless legs syndrome](#) received ongoing treatment with [zolpidem](#) 10 mg daily. Following an average of 4 days of [zolpidem](#) therapy, all patients reported complete relief of symptoms and at one-year follow-up there was no evidence of [relapse](#). Symptoms in 2 patients returned when they stopped treatment after 1 year; however, when [zolpidem](#) was resumed, the symptoms resolved again within a few days. No adverse events were reported. Larger, controlled studies are needed to confirm these findings [27].

4.5.A.10] [Spinocerebellar ataxia](#)

a) Overview

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

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

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

b) Summary:

In a case series, [zolpidem](#) transiently improved the symptoms of [type 2 spinocerebellar ataxia](#) in 4 of 5 patients [28].

c) Adult:

1j) In a case series involving 5 family members, 10 mg of [zolpidem](#) transiently improved the symptoms of [type 2 spinocerebellar ataxia](#) in 4 patients within 1 hour of administration. Patients had experienced a variety of symptoms (eg, titubation, dizziness, loss of balance, deteriorating speech and handwriting, gait ataxia, intention tremor, dysdiadochokinesis) for between 2 to 15 years. Response to [zolpidem](#) ranged from no response to moderate improvement in ataxia, intention tremor, and titubation. Prior to [zolpidem](#) administration, all patients demonstrated hypoperfusion in the vermis or in a cerebellar hemisphere. In 1 patient, this hypoperfusion normalized after the administration of [zolpidem](#) [28].

4.5.A.11] [Supranuclear paralysis](#)

a) 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](#)

b) Summary:

Somewhat effective in one small study in patients with probable [supranuclear palsy](#) [29]

c) Adult:

1) Patients with probable [supranuclear palsy](#) (n=10) demonstrated some improvement with [zolpidem](#). Patients were given single oral doses of [zolpidem](#) 5 mg, 10 mg, [levodopa/carbidopa](#) 250 mg/25 mg, and placebo in random order. Improvement of voluntary eye movement defined as a clinically detectable increase of speed or range of voluntary saccadian eye movements were seen in the [zolpidem](#) patients only. Using the Unified [Parkinson's Disease](#) Rating Scale part III, at 2 hours post-dose, a significant difference over baseline was noted only with [zolpidem](#) 5 mg (p=0.025). These beneficial effects were noted at 40 to 60 minutes after administration and lasted 2 hours. Adverse effects of [zolpidem](#) included drowsiness and increased postural instability [29].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A] Benzodiazepine

4.6.A.1] [Hip fracture](#)

a) Use of [zolpidem](#), benzodiazepines, antipsychotic drugs, and antidepressants by the elderly (mean age 82 years) were all associated with significantly increased risk of [hip fracture](#). In a large, case-control study (1222 cases, 4888 controls), odds ratios of [hip fracture](#) (adjusted for age, gender, race, comorbid illness severity, prior use of other psychoactive medications, prior hospitalization, and prior nursing home use) were 1.95 (95% confidence interval (CI)=1.09-3.51) for [zolpidem](#), 1.46 (CI=1.21-1.76) for benzodiazepines, 1.61 (CI=1.29-2.01) for antipsychotic medications, and 1.46 (CI=1.22-1.75) for antidepressants. Differences among the classifications did not reach statistical significance [151].

4.6.B] Flunitrazepam

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

a) [Zolpidem](#) 20 milligrams nightly was similar in efficacy to flunitrazepam 2 milligrams nightly in the management of insomnia in 42 female inpatients in a double-blind, controlled study. Side effects were similar in nature and frequency in the 2 treatment groups [156].

b) Double-blind study; 30 patients on antidepressant therapy with insomnia refractory to [clomipramine](#) administration were treated for 15 days with [zolpidem](#) 10 milligrams (mg) or flunitrazepam 1 mg orally every evening; both treatments resulted in a significant reduction of insomnia, using the Stanford Sleepiness Scale (SSS) and the Saint Mary Hospital Sleep Questionnaire (SMHSQ). For [zolpidem](#) the SSS score decreased from 3.8 to 2.2 (p less than 0.001) and the SMHSQ item time of sleep latency from 111 to 17 minutes (p less than 0.001); the Hamilton Rating Scale for Depression and the Hamilton Rating Scale for Anxiety showed improvement (scores from 26.7 to 10.6, and from 22.1 to 8.2, respectively; p less than 0.001). After discontinuation, scores reached baseline by the 10th day [157].

c) Morning-after residual [sequelae](#) were observed with flunitrazepam 2 mg, but not [zolpidem](#) 20 mg, when each was given at bedtime to 12 normal male subjects in a randomized study [158].

4.6.C] [Lormetazepam](#)

1) Adverse Effects

a) Low-dose zopiclone and lormetazepam, but not [zolpidem](#), negatively affected body sway 8 hours post-dose in elderly patients. In addition, [zolpidem](#) appeared to have fewer effects on short-term and working memory performance. In a single-center, double-blind, cross-over trial, healthy patients age 65 years or older (n=48) were randomized to receive a single dose of [zolpidem](#) 5 milligrams (mg), zopiclone 3.75 mg, lormetazepam 1 mg, or placebo. Using computerized assessment of body sway

on a stabilometric platform, investigators noted a significantly increased body sway with all active drugs compared to placebo up to 5 hours post-dose (p less than 0.05 for all measures). For testing performed with patients' eyes open, effects were sustained at 8 hours post-dose with lormetazepam ($p=0.0228$) and zopiclone ($p=0.0237$), but not with [zolpidem](#); however, when tested with their eyes closed, [zolpidem](#) ($p=0.0012$) was the only agent that significantly affected body sway. By 10 hours post-dose, no differences were noted with any active drugs. Memory performance based on the Sternberg memory scanning test was significantly impaired with lormetazepam and zopiclone (p less than 0.05 for each) but not with [zolpidem](#); only lormetazepam significantly decreased the percentage of good responses, however ($p=0.0174$). No drugs significantly affected immediate free recall, but all drugs significantly and negatively affected delayed free recall ($p=0.0394$). All agents were superior to placebo for improving sleep.

4.6.D] [Midazolam](#)

4.6.D.1] Sedation

a) [Zolpidem](#) 20 milligrams (mg) and [midazolam](#) 15 mg had similar sleep-inducing effects, [anterograde amnesia](#), and side effects in a study of 93 patients undergoing surgery [159]. However, alertness and concentration were significantly reduced in the [zolpidem](#) group compared with the [midazolam](#) group 60 minutes after administration.

4.6.E] [Phenobarbital](#)

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

a) In a randomized, double-blind study of 304 patients undergoing elective surgery, [zolpidem](#) 8.03 milligrams orally for anesthetic premedication produced significantly more irritability, aggressive behavior and negative mood than did [phenobarbital](#) 100 milligrams orally in multi-dimensional psychological testing [160]. Both drugs in combination with oral [promethazine](#) 50 milligrams produced greater deactivation (more fatigue, numbness and drowsiness) as compared to placebo, and patients pretreated with [promethazine](#) required significantly less [thiopental](#) for [induction of anesthesia](#) than did the patients in the [zolpidem](#) group. All drugs were administered approximately 2200 hours the evening before surgery and mood evaluations were conducted five separate times prior to surgery. [Zolpidem](#) may have advantages to [phenobarbital](#) for preoperative sedation (no induction of microsomal liver enzymes, shorter duration of effect); however, the increase in expressions of hostility with [zolpidem](#) compared to [phenobarbital](#) must be kept in mind.

4.6.F] [Temazepam](#)

1) Efficacy

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

4.6.G] Trazodone

4.6.G.1] Insomnia

a) **Zolpidem** 10 milligrams (mg) was slightly superior to **trazodone** 50 mg in reducing sleep latency and increasing sleep duration in a 2-week, randomized, parallel-group, double-blind comparative study (n=278). The periods of sleep latency at the end of week 1 were 48.2 minutes and 57.7 minutes for the groups treated with **zolpidem** or **trazodone**, respectively (p less than 0.037), but did not differ significantly at the end of week 2 (64.7 minutes versus 54.5 minutes, respectively). The sleep duration was significantly higher in both groups compared to the group treated with placebo (p=0.001). Patients treated with **zolpidem** reported longer sleep durations at week 1 than those treated with **trazodone** (378.8 minutes versus 366.4 minutes, respectively) with a trend toward significance (p less than 0.060), but virtually no difference between drugs at week 2. The reduction in clinical significance in both parameters with both drugs, compared with placebo, was primarily due to improvement in the placebo-treated group over time while the level of improvement with both drugs was essentially unchanged in the second week of treatment. Because of the slightly shorter period of sleep latency, **zolpidem** may have some advantages over **trazodone** in the treatment of **primary insomnia** [152].

4.6.H] Triazolam

4.6.H.1] Insomnia

a) **Zolpidem** was shown to be as safe and effective as **triazolam** in the treatment of psychiatric patients with sleep disorders. The doses studied were **zolpidem** 20 milligrams and **triazolam** 0.5 milligram [153].
 b) **Zolpidem**, a hypnotic of a new chemical class (the imidazopyridines), was reported to be at least as effective as **triazolam** in geriatric insomniac patients. **Zolpidem**, 5 milligrams and 10 milligrams, demonstrated a good safety profile [154].

4.6.H.2) Adverse Effects

a) The non-benzodiazepine hypnotic drug, **zolpidem**, given at a single equivalent dose, had no significant effect on arterial blood gases and control of breathing in 12 **severe chronic obstructive pulmonary disease** (COPD) patients, in contrast to **triazolam** and flunitrazepam [155].

4.6.I] Zaleplon

4.6.I.1] Insomnia

a) GENERAL INFORMATION: **Zaleplon** 20 milligrams has comparable adverse psychomotor effects to **zolpidem** 10 mg [161].
 b) **Zaleplon** 10 and 20 milligrams (mg) decreased sleep latency for up to 4 weeks while **zolpidem** 10 mg decreased sleep latency for up to 3 weeks as compared to placebo [162]. Patients were randomly assigned to receive **zaleplon** 5 mg (n=122), **zaleplon** 10 mg (n=121), **zaleplon** 20 mg (n=124), **zolpidem** 10 mg (n=122), or placebo (n=126) for 28 days. Sleep latency was significantly reduced with **zaleplon** 20 mg during weeks 1 through 4 (p less than 0.001 for weeks 1 to 3, p less than 0.01 for week 4), and similarly with **zaleplon** 10 mg during weeks 1 through 4 (p less than 0.001 for week 1, p less than 0.01 for weeks 2 and 3, p less than 0.05 for week 4). **Zaleplon** 5 mg reduced sleep latency during weeks 1 through 3 (p less than 0.05 for week 1, and p less than 0.01 for weeks 2 and 3). **Zolpidem** 10 mg also reduced sleep latency during weeks 1 through 3 (p less than 0.05 for weeks 1 and 3 and p less than 0.01 for week 2). Sleep duration was increased significantly only by **zaleplon** 20 mg during weeks 1, 2, and 4 (p less than 0.05). **Zolpidem** 10 mg significantly increased sleep duration during all 4 weeks (p less than 0.001). No significant differences were observed in number of awakenings between placebo and any of the active treatment groups. On the first

night of discontinuation, there were no significant differences seen between [zaleplon](#) and placebo. With [zolpidem](#), significant differences were seen on the first night of discontinuation in sleep latency (p less than 0.001), sleep duration (p less than 0.05), and in number of awakenings (p less than 0.01).

c) In 31 patients with mild to [moderate chronic obstructive pulmonary disease](#) and insomnia, [zaleplon](#) and [zolpidem](#) were safe and effective for sleep-onset insomnia [163]. Patients received [zaleplon](#) 10 milligrams, [zolpidem](#) 10 mg, and placebo for 1 night each in random order. Patients reported improvement in sleep latency with both drugs and total sleep time for [zolpidem](#) only. No differences were seen in mean overnight arterial [oxygen saturation](#) or with percent of night with saturation less than 90% for [zaleplon](#), [zolpidem](#), or placebo.

d) [Zaleplon](#) and [zolpidem](#) were both subjectively effective in elderly patients with sleep onset insomnia [164]. In a double-blind study, 549 elderly patients (65-years-old or older) were randomized to [zaleplon](#) 5 or 10 milligrams, [zolpidem](#) 5 mg, or placebo for 2 weeks of treatment. Subjective sleep latency was significantly decreased for [zaleplon](#) 10 mg during both week 1 and week 2 (both weeks p less than 0.001), but only for week 2 for [zaleplon](#) 5 mg (p less than 0.001). Subjective sleep latency was significantly decreased for [zolpidem](#) during both week 1 and week 2 (p less than 0.05, p less than 0.005, respectively). Subjective total sleep time was significantly increased for [zaleplon](#) 10 mg during week 1 only (p less than 0.05) and for [zolpidem](#) during week 1 and week 2 (p less than 0.001, p less than 0.01, respectively). The number of awakenings did not differ for either dose of [zaleplon](#), but was reduced by [zolpidem](#) during both weeks.

4.6.I.2) Adverse Effects

a) [Zaleplon](#) had fewer detrimental effects on memory, learning, and psychomotor performance than did [zolpidem](#) or [triazolam](#) in healthy subjects. In a double-blind crossover study, 24 healthy subjects received placebo, [zaleplon](#) 10 milligrams (mg), [zaleplon](#) 20 mg, [zolpidem](#) 10 mg, [zolpidem](#) 20 mg, [triazolam](#) 0.25 mg, and placebo in 6 separate, single-dose, nighttime sessions. At 1.25 hours after dosing, statistically significant differences (p less than 0.05) in psychomotor performance were seen with [zaleplon](#) 20 mg, [zolpidem](#) 10 mg and 20 mg, and [triazolam](#) when compared with the results with placebo. Memory and cognitive tests showed no differences at 1.25 hours between [zaleplon](#) 10 mg and placebo. Memory was similarly impaired for [zolpidem](#) 10 mg and [triazolam](#) 0.25 mg, but that dose of [zolpidem](#) produced greater learning impairment than did [triazolam](#). At 8.25 hours post-dosing, [zaleplon](#) 10 mg, [zaleplon](#) 20 mg, and [zolpidem](#) 10 mg showed differences from placebo only in the Delayed Word Recall Test and Digit-Symbol Substitution Test. Central nervous system (CNS) adverse events occurred with 17% of sessions with placebo, 48% of sessions with [zaleplon](#) 10 mg, and 71% to 74% of sessions with each of the other treatments [165].

b) [Zaleplon](#) produced neither objective nor subjective residual effects when administered as little as 2 hours before awakening [166]. In contrast [zolpidem](#) residual effects were seen up to 5 hours after administration. Subjects were awakened and administered [zaleplon](#) 10 mg, [zolpidem](#) 10 mg, or placebo at 5, 4, 3, or 2 hours before awakening. In the morning a battery of subjective and objective assessments were administered. [Zaleplon](#) regardless of administration time did not significantly impair psychomotor performance, arousal and cognitive function, or memory function as compared to placebo. [Zolpidem](#) significantly impaired Digit-Symbol-Substitution Test when administered at 2, 3, and 5 hours before awakening (p less than 0.05, 0.001, 0.05, respectively). It also impaired memory as measured by number of words correct on immediate recall at 2, 3, 4, and 5 hours post-administration (p less than 0.001 for all). Delayed recall was also impaired as measured by number of words correct on delayed recall at 2, 3, 4, and 5 hours post-administration (p less than 0.001 for 2 to 4 hours, and p less than 0.01 for 5 hours).

4.6.J] Zopiclone

1j) Adverse Effects

a) Low-dose zopiclone and lormetazepam, but not **zolpidem**, negatively affected body sway 8 hours post-dose in elderly patients. In addition, **zolpidem** appeared to have fewer effects on short-term and working memory performance. In a single-center, double-blind, cross-over trial, healthy patients age 65 years or older (n=48) were randomized to receive a single dose of **zolpidem** 5 milligrams (mg), zopiclone 3.75 mg, lormetazepam 1 mg, or placebo. Using computerized assessment of body sway on a stabilometric platform, investigators noted a significantly increased body sway with all active drugs compared to placebo up to 5 hours post-dose (p less than 0.05 for all measures). For testing performed with patients' eyes open, effects were sustained at 8 hours post-dose with lormetazepam (p=0.0228) and zopiclone (p=0.0237), but not with **zolpidem**; however, when tested with their eyes closed, **zolpidem** (p=0.0012) was the only agent that significantly affected body sway. By 10 hours post-dose, no differences were noted with any active drugs. Memory performance based on the Sternberg memory scanning test was significantly impaired with lormetazepam and zopiclone (p less than 0.05 for each) but not with **zolpidem**; only lormetazepam significantly decreased the percentage of good responses, however (p=0.0174). No drugs significantly affected immediate free recall, but all drugs significantly and negatively affected delayed free recall (p=0.0394). All agents were superior to placebo for improving sleep.

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