



Medicaid Drug Use Criteria

Benzodiazepines (Nonsedative/ Hypnotics)

Note: Sedative/hypnotic benzodiazepines included in Sedative/Hypnotics criteria.

- Developed October 1993.
- Revised March 2020; March 2018; May 2017; December 2014; March 2013; June 2011; January 2009; April 2003; December 2001; December 2000; December 1999; November 1998; November 1997; December 1996.

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

1.1 Adults

Non-sedative/hypnotic benzodiazepines are FDA-approved for use in the outpatient setting to manage anxiety (alprazolam, chlordiazepoxide, clorazepate, oral diazepam, lorazepam, oxazepam), panic disorder (alprazolam, clonazepam), acute musculoskeletal (MS) conditions including spasticity (oral diazepam), seizures [clobazam (Lennox-Gastaut syndrome), clonazepam, clorazepate, nasal, oral and rectal diazepam], and acute alcohol withdrawal (chlordiazepoxide, clorazepate, oral diazepam, oxazepam).^[1-10] The FDA has approved a new dosage formulation for clobazam, an oral film (Sympazan®), for adjunctive seizure management in Lennox-Gastaut syndrome.^[11] A new diazepam nasal formulation (Valtoco®) has been FDA-approved for use in adult patients to treat intermittent frequent seizure episodes that differ from a patient's usual seizure pattern.^[12] The chlordiazepoxide-amitriptyline combination is indicated for depression with associated anxiety symptoms, while chlordiazepoxide/clidinium is FDA-approved for emotional factor control in gastrointestinal disorders as well as adjunctive use in peptic ulcer disease and irritable bowel syndrome.^[13, 14] Tables 1 and 2 summarize the adult maximum recommended dosages for non-sedative/hypnotic benzodiazepines as monotherapy and combination therapy.

Table 1. Adult Benzodiazepine Maximum Recommended Daily Dosages: Monotherapy^[1-12]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
alprazolam (Xanax®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg tablets, disintegrating tablets; 0.5 mg, 1 mg, 2 mg, 3 mg extended-release tablets; 1 mg/ml oral solution	anxiety	Less than or equal to and greater than 65 years: 4 mg daily
alprazolam		panic	Less than or equal to and greater than 65 years: 10 mg daily
chlordiazepoxide (generics)	5 mg, 10 mg, 25 mg capsule	alcohol withdrawal (AW)	Less than or equal to and greater than 65 years: 300 mg daily, in divided doses

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide		anxiety	Less than or equal to 65 years: mild, moderate: 40 mg daily severe: 100 mg daily greater than 65 years: 20 mg daily
clobazam (Onfi®, generics, Sympazan®)	10 mg, 20 mg tablets; 2.5 mg/mL suspension; 5 mg, 10 mg, 20 mg oral soluble film	seizures associated with Lennox- Gastaut syndrome	Less than or equal to 65 years: 40 mg/day in two divided doses greater than 65 years: 20 mg/day in two divided doses (weights Less than or equal to 30 kg) 40 mg/day in two divided doses (weights greater than 30 kg)
clonazepam (Klonopin®, generics)	0.5 mg, 1 mg, 2 mg tablets; 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg disintegrating tablets	panic	Less than or equal to and greater than 65 years: 4 mg daily
clonazepam		seizures	Less than or equal to and greater than 65 years: 20 mg daily
clorazepate (Tranxene®, generics)	3.75 mg, 7.5 mg, 15 mg tablets	AW	Less than or equal to and greater than 65 years: 90 mg daily
clorazepate		anxiety	Less than or equal to and greater than 65 years: 60 mg daily
clorazepate		seizures	Less than or equal to and greater than 65 years: 90 mg daily
diazepam (nasal) (Valtoco®)	5 mg as one 5 mg device, 10 mg as one 10 mg device, 15 mg as 2 x 7.5 mg devices, 20 mg as 2 x 10 mg devices nasal liquid	seizures	28-50 kg [^] : 10 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 51-75 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose) greater than or equal to 76 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose)
diazepam (oral) (Valium®, generics)	2 mg, 5 mg, 10 mg oral tablets; 5 mg/mL, 5 mg/5 mL oral solution	AW	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		anxiety	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		musculoskeletal conditions	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		seizures	Less than or equal to and greater than 65 years: 40 mg daily

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
diazepam (rectal) (Valium®, generics)	2.5 mg, 10 mg, 20 mg rectal gel	seizures	Less than or equal to and greater than 65 years: 0.2 mg/kg; may be repeated once 4-12 hours after initial dose
lorazepam (Ativan®, generics)	0.5 mg, 1 mg, 2 mg tablets; 2 mg/mL solution	anxiety	Less than or equal to and greater than 65 years: 10 mg daily, in divided doses
oxazepam (Serax®, generics)	10 mg, 15 mg, 30 mg capsule	AW	Less than or equal to 65 years: 120 mg daily in divided doses greater than 65 years: 60 mg daily in divided doses#
oxazepam		anxiety	Less than or equal to 65 years: mild, moderate: 60 mg daily in divided doses severe: 120 mg daily in divided doses greater than 65 years: 40 mg daily in divided doses

- * benzodiazepine doses should be reduced to lowest effective dose, if possible, in elderly (patients greater than 65 years of age), to minimize oversedation; these patients more sensitive to pharmacologic effects of these agents
- + Dose rounded up to nearest commercially available dose (in multiples of 2.5 mg); should not be administered by caregivers outside the hospital more frequently than one course every 5 days with a maximum of 5 courses per month; not for chronic administration to minimize potential for development of tolerance
- # in elderly patients, doses up to 120 mg/day may be needed to treat AW
- ^ may give second diazepam nasal dose at least 4 hours after first dose, if necessary; may not use more than 2 doses to treat single episode; may not treat more than 1 episode/5 days or more than 5 episodes/month

Table 2. Adult Benzodiazepine Maximum Recommended Dosages: Combination Therapy^[1-7, 13, 14]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide/ amitriptyline (Limbitrol®, generics)	5 mg/12.5 mg tablets 10 mg/25 mg double-strength tablets	depression with concurrent anxiety symptoms	60 mg chlordiazepoxide/ 150 mg amitriptyline daily in divided doses

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide/ clidinium (Librax®, generics)	5 mg/ 2.5 mg capsule	emotional/ somatic factors in gastro- intestinal disorders; adjunctive therapy in peptic ulcer disease or irritable bowel syndrome	40 mg/20 mg per day (2 capsules 4 times daily)

1.2 Pediatrics

Safety and effectiveness of alprazolam and combination therapies, chlordiazepoxide/amitriptyline and chlordiazepoxide/clidinium, in children less than 18 years of age have not been established. [1-5, 9, 13, 14]

Clobazam has recently been approved in children 2 years of age and older to manage seizures associated with Lennox-Gastaut syndrome. [1-5, 10] The FDA has approved a new dosage formulation for clobazam, an oral film (Sympazan®), for adjunctive seizure management in Lennox-Gastaut syndrome in patients 2 years and older. [11] A new diazepam nasal formulation (Valtoco®) has been FDA-approved for use in patients 6 years and older to treat intermittent frequent seizure episodes that differ from a patient's usual seizure pattern. [12]

With the exception of alprazolam, non-sedative/hypnotic benzodiazepines are indicated for use in pediatric patients to manage anxiety or seizures. Pediatric dosages and age limitations for benzodiazepines are summarized in Table 3.

Table 3. Pediatric Benzodiazepine Maximum Recommended Dosages^[1-12]

Drug Name	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide	alcohol withdrawal (AW)	adolescents greater than or equal to 12 years: 300 mg daily in divided doses
chlordiazepoxide	anxiety	greater than or equal to 6 years: 30 mg daily in divided doses
clobazam	seizures associated with Lennox-Gastaut syndrome	2 years and older, adolescents Less than or equal to 30 kg: 20 mg/day in two divided doses 2 years and older, adolescents greater than 30 kg: 40 mg/day in two divided doses
clonazepam	seizures	Less than 10 years or Less than or equal to 30 kg: 0.2 mg/kg daily in divided doses greater than or equal to 10 years or greater than 30 kg: 20 mg daily in divided doses
clorazepate	seizures	9-12 years: 60 mg daily in divided doses greater than 12 years: 90 mg daily in divided doses

Drug Name	Treatment Indication	Maximum Recommended Dosage
diazepam (nasal)	seizures	6-11 years of age: 10-18 kg: 5 mg as one spray in one nostril (equates to 0.3 mg/kg dose) 19-37 kg [^] : 10 mg as one spray in one nostril (equates to 0.3 mg/kg dose) 38-55 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.3 mg/kg dose) 56-74 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.3 mg/kg dose) greater than or equal to 12 years of age: 14-27 kg: 5 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 28-50 kg [^] : 10 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 51-75 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose) greater than or equal to 76 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose)
diazepam (oral)	musculoskeletal conditions	greater than or equal to 6 months of age: 10 mg/day in divided doses have been used; dose may be increased as needed and tolerated – no maximum dose documented
diazepam (oral)	seizures	greater than or equal to 6 months of age: 10 mg/day in divided doses have been used; dose may be increased as needed and tolerated – no maximum dose documented
diazepam (rectal)	seizures+	2-5 years: 0.5 mg/kg/dose 6-11 years: 0.3 mg/kg/dose greater than or equal to 12 years: 0.2 mg/kg/dose
lorazepam	anxiety	greater than or equal to 12 years: 10 mg daily in divided doses (maximum, 2 mg/dose)
oxazepam	anxiety	6-12 years: dose not established; 1 mg/kg/day in divided doses has been adequate greater than 12 years: mild, moderate: 60 mg daily, in divided doses severe: 120 mg daily, in divided doses

- + Dose rounded up to nearest commercially available dose (in multiples of 2.5 mg); should not be administered by caregivers outside the hospital more frequently than one course every 5 days with a maximum of 5 courses per month; not for chronic administration to minimize potential for development of tolerance
- [^] may give second diazepam nasal dose at least 4 hours after first dose, if necessary; may not use more than 2 doses to treat single episode; may not treat more than 1 episode/5 days or more than 5 episodes/month

2 Duration of Therapy^[1-27]

Anxiety disorders are considered chronic disorders with low spontaneous remission rates and high rates of relapse. Pharmacotherapy for generalized anxiety disorder (GAD) in adults includes antidepressants, benzodiazepines, buspirone, hydroxyzine and pregabalin. Treatment duration for GAD ranges from 3 to 12 months to accomplish treatment goals of symptom remission and improvement in quality of life. Although antidepressants are now considered drugs of choice for managing GAD, benzodiazepines are used frequently for short-term management of anxiety, as an adjunct to initiating antidepressant therapy, or improvement in sleep disturbances associated with GAD and/or antidepressant therapy. Benzodiazepines provide symptom improvement more rapidly than antidepressants and are more effective in managing somatic complaints rather than psychic symptoms. Although longer-term use is considered relatively safe and effective for benzodiazepines, the potential for abuse, dependence and withdrawal does exist.

In pediatric patients, selective serotonin reuptake inhibitors (SSRIs) are agents of choice to manage childhood anxiety disorders, with benzodiazepines prescribed as alternatives either alone or concurrently with accepted antidepressant therapy.

Panic disorder (PD) is a chronic, recurring condition requiring drug therapy suitable for prolonged use. The acute treatment phase for PD lasts approximately 12 weeks, and most patients require an additional 12 to 18 months of therapy to optimize treatment response and prevent relapse. SSRIs are the agents of choice to manage PD, although benzodiazepines are frequently prescribed as well, usually in combination with antidepressant therapy. While benzodiazepines are effective in the short-term treatment of panic disorder due to rapid onset of action, long-term treatment may be less desirable due to the potential for dependence. Unlike anxiety disorder patients, patients with panic disorder are less successful at discontinuing benzodiazepine therapy. Additionally, there is a high prevalence of comorbid depression and/or bipolar disorder in patients with panic disorder. Benzodiazepines are less effective than other available agents when panic disorder coexists with other mood disorders. Therefore, patients with panic disorder and other psychiatric comorbidities may benefit from short-term therapy with a benzodiazepine, with chronic management incorporating mood stabilizing or antidepressant agents that are also effective in panic disorder. Alprazolam has been studied more than other available benzodiazepines for the treatment of panic disorder, although

clonazepam, lorazepam, and diazepam have also been evaluated. Most studies evaluating benzodiazepine use in panic disorder have been short-term studies (Dosage

2.1 Adults

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Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
alprazolam (Xanax®, generics)	0.25 mg, 0.5 mg, 1 mg, 2 mg tablets, disintegrating tablets; 0.5 mg, 1 mg, 2 mg, 3 mg extended-release tablets; 1 mg/ml oral solution	anxiety	Less than or equal to and greater than 65 years: 4 mg daily
alprazolam		panic	Less than or equal to and greater than 65 years: 10 mg daily
chlordiazepoxide (generics)	5 mg , 10 mg, 25 mg capsule	alcohol withdrawal (AW)	Less than or equal to and greater than 65 years: 300 mg daily, in divided doses

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide		anxiety	Less than or equal to 65 years: mild, moderate: 40 mg daily severe: 100 mg daily greater than 65 years: 20 mg daily
clobazam (Onfi®, generics, Sympazan®)	10 mg, 20 mg tablets; 2.5 mg/mL suspension; 5 mg, 10 mg, 20 mg oral soluble film	seizures associated with Lennox- Gastaut syndrome	Less than or equal to 65 years: 40 mg/day in two divided doses greater than 65 years: 20 mg/day in two divided doses (weights Less than or equal to 30 kg) 40 mg/day in two divided doses (weights greater than 30 kg)
clonazepam (Klonopin®, generics)	0.5 mg, 1 mg, 2 mg tablets; 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg disintegrating tablets	panic	Less than or equal to and greater than 65 years: 4 mg daily
clonazepam		seizures	Less than or equal to and greater than 65 years: 20 mg daily
clorazepate (Tranxene®, generics)	3.75 mg, 7.5 mg, 15 mg tablets	AW	Less than or equal to and greater than 65 years: 90 mg daily
clorazepate		anxiety	Less than or equal to and greater than 65 years: 60 mg daily
clorazepate		seizures	Less than or equal to and greater than 65 years: 90 mg daily
diazepam (nasal) (Valtoco®)	5 mg as one 5 mg device, 10 mg as one 10 mg device, 15 mg as 2 x 7.5 mg devices, 20 mg as 2 x 10 mg devices nasal liquid	seizures	28-50 kg [^] : 10 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 51-75 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose) greater than or equal to 76 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose)
diazepam (oral) (Valium®, generics)	2 mg, 5 mg, 10 mg oral tablets; 5 mg/mL, 5 mg/5 mL oral solution	AW	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		anxiety	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		musculoskeletal conditions	Less than or equal to and greater than 65 years: 40 mg daily
diazepam (oral)		seizures	Less than or equal to and greater than 65 years: 40 mg daily

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
diazepam (rectal) (Valium®, generics)	2.5 mg, 10 mg, 20 mg rectal gel	seizures	Less than or equal to and greater than 65 years: 0.2 mg/kg; may be repeated once 4-12 hours after initial dose
lorazepam (Ativan®, generics)	0.5 mg, 1 mg, 2 mg tablets; 2 mg/mL solution	anxiety	Less than or equal to and greater than 65 years: 10 mg daily, in divided doses
oxazepam (Serax®, generics)	10 mg, 15 mg, 30 mg capsule	AW	Less than or equal to 65 years: 120 mg daily in divided doses greater than 65 years: 60 mg daily in divided doses#
oxazepam		anxiety	Less than or equal to 65 years: mild, moderate: 60 mg daily in divided doses severe: 120 mg daily in divided doses greater than 65 years: 40 mg daily in divided doses

- * Benzodiazepine doses should be reduced to lowest effective dose, if possible, in elderly (patients greater than 65 years of age), to minimize oversedation; these patients more sensitive to pharmacologic effects of these agents
- + Dose rounded up to nearest commercially available dose (in multiples of 2.5 mg); should not be administered by caregivers outside the hospital more frequently than one course every 5 days with a maximum of 5 courses per month; not for chronic administration to minimize potential for development of tolerance
- # in elderly patients, doses up to 120 mg/day may be needed to treat AW
- ^ May give second diazepam nasal dose at least 4 hours after first dose, if necessary; may not use more than 2 doses to treat single episode; may not treat more than 1 episode/5 days or more than 5 episodes/month

Table 2. Adult Benzodiazepine Maximum Recommended Dosages: Combination Therapy^[1-7, 13, 14]

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide/ amitriptyline (Limbitrol®, generics)	5 mg/12.5 mg tablets 10 mg/25 mg double-strength tablets	depression with concurrent anxiety symptoms	60 mg chlordiazepoxide/ 150 mg amitriptyline daily in divided doses

Drug Name	Dosage Form/ Strength	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide/ clidinium (Librax®, generics)	5 mg/ 2.5 mg capsule	emotional/ somatic factors in gastro- intestinal disorders; adjunctive therapy in peptic ulcer disease or irritable bowel syndrome	40 mg/20 mg per day (2 capsules 4 times daily)

2.2 Pediatrics

Safety and effectiveness of alprazolam and combination therapies, chlordiazepoxide/amitriptyline and chlordiazepoxide/clidinium, in children less than 18 years of age have not been established.^[1-5, 9, 13, 14]

Clobazam has recently been approved in children 2 years of age and older to manage seizures associated with Lennox-Gastaut syndrome.^[1-5, 10] The FDA has approved a new dosage formulation for clobazam, an oral film (Sympazan®), for adjunctive seizure management in Lennox-Gastaut syndrome in patients 2 years and older.^[11] A new diazepam nasal formulation (Valtoco®) has been FDA-approved for use in patients 6 years and older to treat intermittent frequent seizure episodes that differ from a patient's usual seizure pattern.^[12]

With the exception of alprazolam, non-sedative/hypnotic benzodiazepines are indicated for use in pediatric patients to manage anxiety or seizures. Pediatric dosages and age limitations for benzodiazepines are summarized in Table 3.

Table 3. Pediatric Benzodiazepine Maximum Recommended Dosages^[1-12]

Drug Name	Treatment Indication	Maximum Recommended Dosage
chlordiazepoxide	alcohol withdrawal (AW)	adolescents greater than or equal to 12 years: 300 mg daily in divided doses
chlordiazepoxide	anxiety	greater than or equal to 6 years: 30 mg daily in divided doses
clobazam	seizures associated with Lennox-Gastaut syndrome	2 years and older, adolescents Less than or equal to 30 kg: 20 mg/day in two divided doses 2 years and older, adolescents greater than 30 kg: 40 mg/day in two divided doses
clonazepam	seizures	Less than 10 years or Less than or equal to 30 kg: 0.2 mg/kg daily in divided doses greater than or equal to 10 years or greater than 30 kg: 20 mg daily in divided doses
clorazepate	seizures	9-12 years: 60 mg daily in divided doses greater than 12 years: 90 mg daily in divided doses

Drug Name	Treatment Indication	Maximum Recommended Dosage
diazepam (nasal)	seizures	6-11 years of age: 10-18 kg: 5 mg as one spray in one nostril (equates to 0.3 mg/kg dose) 19-37 kg [^] : 10 mg as one spray in one nostril (equates to 0.3 mg/kg dose) 38-55 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.3 mg/kg dose) 56-74 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.3 mg/kg dose) greater than or equal to 12 years of age: 14-27 kg: 5 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 28-50 kg [^] : 10 mg as one spray in one nostril (equates to 0.2 mg/kg dose) 51-75 kg [^] : 15 mg as 2 x 7.5 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose) greater than or equal to 76 kg [^] : 20 mg as 2 x 10 mg devices with one spray in each nostril (equates to 0.2 mg/kg dose)
diazepam (oral)	musculoskeletal conditions	greater than or equal to 6 months of age: 10 mg/day in divided doses have been used; dose may be increased as needed and tolerated – no maximum dose documented
diazepam (oral)	seizures	greater than or equal to 6 months of age: 10 mg/day in divided doses have been used; dose may be increased as needed and tolerated – no maximum dose documented
diazepam (rectal)	seizures+	2-5 years: 0.5 mg/kg/dose 6-11 years: 0.3 mg/kg/dose greater than or equal to 12 years: 0.2 mg/kg/dose
lorazepam	anxiety	greater than or equal to 12 years: 10 mg daily in divided doses (maximum, 2 mg/dose)
oxazepam	anxiety	6-12 years: dose not established; 1 mg/kg/day in divided doses has been adequate greater than 12 years: mild, moderate: 60 mg daily, in divided doses severe: 120 mg daily, in divided doses

- +Dose rounded up to nearest commercially available dose (in multiples of 2.5 mg); should not be administered by caregivers outside the hospital more frequently than one course every 5 days with a maximum of 5 courses per month; not for chronic administration to minimize potential for development of tolerance
- [^]may give second diazepam nasal dose at least 4 hours after first dose, if necessary; may not use more than 2 doses to treat single episode; may not treat more than 1 episode/5 days or more than 5 episodes/month

3 Duplicative Therapy

The combined use of two or more benzodiazepines is not supported in the literature and therefore is not recommended. The concurrent use of two or more benzodiazepines will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for nonsedative/hypnotic benzodiazepines are summarized in Table 4. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 4. Benzodiazepine (nonsedative/hypnotic) Drug-Drug Interactions^[1-5, 7-14]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
alprazolam	CYP3A4 inhibitors (e.g., azole anti-fungals, macrolides, NNRT inhibitors, protease inhibitors)	adjunctive administration may result in enhanced oxidized BZD pharmacologic effects and/or toxicity, including significant sedation and/or respiratory depression, as alprazolam is metabolized by CYP3A4	avoid combined therapy with most CYP3A4 inhibitors, if possible	contraindicated - azole antifungals, NNRT inhibitors, protease inhibitors; moderate - macrolides (DrugReax) 1 – severe (azole antifungals, NNRT inhibitors, protease inhibitors); 3-moderate (macrolides) (CP)
alprazolam	phenytoin	combined use may induce alprazolam metabolism and decrease alprazolam pharmacologic effects	monitor for reduced alprazolam clinical effects and adjust doses as necessary	3-moderate (CP)
benzodiazepines (BZDs)	central nervous system (CNS) depressants	concurrent administration may potentiate respiratory depression, especially with overdosage	monitor for respiratory depression; adjust doses as necessary	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
BZDs	sodium oxybate (Xyrem®)	combined use may lead to increased respiratory depression due to additive CNS/respiratory depressive effects	adjunctive use should be avoided; if concurrent use necessary, closely monitor for respiratory depression; dosage reductions for one or both medications may be needed	major (DrugReax) 1-severe (CP)
clobazam	drugs metabolized by CYP2C19 (e.g., clopidogrel, cimetidine, fluconazole)	co-administration may result in increased clobazam serum levels and increased pharmacologic and/or adverse effects as clobazam is partially metabolized by CYP2C19	monitor for enhanced clobazam pharmacologic/adverse effects; adjust clobazam dose as necessary	moderate (DrugReax) 3-moderate (CP)
other oxidized BZDs (chlor-diazepoxide, clonazepam, diazepam)	CYP3A4 inhibitors [e.g., azole antifungals, macrolides, non-nucleoside reverse transcriptase (NNRT) inhibitors, protease inhibitors]	adjunctive administration may result in enhanced oxidized BZD pharmacologic effects and/or toxicity, including significant sedation and/or respiratory depression, as oxidized BZDs are metabolized by CYP3A4	avoid combined therapy, if possible; if concurrent with BZD necessary, monitor for increased sedation, respiratory depression, or consider a BZD metabolized by glucuronidation (e.g., oxazepam)	moderate (DrugReax) 2-major (protease inhibitors); 3-moderate (azoles, macrolides, NNRT inhibitors) (CP)
oxidized BZDs (e.g., alprazolam, chlordiazepoxide, clonazepam, diazepam)	CYP3A4 inducers (e.g., carbamazepine, rifamycins)	combined use may result in increased oxidized BZD clearance, reduced oxidized BZD serum levels, and decreased pharmacologic effects; oxidized BZDs are metabolized by CYP3A4	monitor oxidized BZD clinical response and adjust dose as needed; may also consider substituting a BZD metabolized by glucuronidation (e.g., oxazepam)	moderate (DrugReax) 2-major, 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level*
select BZDs (chlordiazepoxide, diazepam)	phenytoin	concomitant use may result in unpredictable effects on serum phenytoin levels (may increase, decrease, or not change) due to unknown effect on phenytoin metabolism; phenytoin may induce BZD metabolism, reduce BZD serum levels, and decrease BZD pharmacologic effects	closely monitor serum phenytoin levels and observed for altered pharmacologic effects (reduced efficacy, increased toxicity); monitor for reduced BZD clinical effects and adjust doses as necessary	major (diazepam), moderate (chlordiazepoxide) (DrugReax) 3-moderate (CP)
chlordiazepoxide/ amitriptyline	amphetamines	combined administration may increase potential for serotonin syndrome as both medications target the serotonin neurotransmitter system	if adjunctive therapy is necessary, start with lower doses and monitor for signs/ symptoms of serotonin syndrome; discontinue both medications if serotonin syndrome develops	major (DrugReax) 2-major (CP)
chlordiazepoxide/ amitriptyline	monoamine oxidase inhibitors	increased risk of serotonin syndrome with amitriptyline (e.g., mental status changes, hyperpyrexia, restless, shivering, hypertonia, tremor) due to serotonin metabolism inhibition by monoamine oxidase	allow 14 days after MAOI discontinuation before initiating other tricyclic antidepressant therapy	contraindicated (DrugReax) 1-severe (CP)
chlordiazepoxide/ amitriptyline	QT interval-prolonging drugs	co-administration with QT interval-prolonging drugs may increase risk of QT interval prolongation and torsades de pointes as amitriptyline also prolongs the QT interval	avoid concurrent use; if adjunctive use necessary, monitor for increased pharmacologic/toxic effects; adjust dose as necessary or discontinue therapy	contraindicated (DrugReax) 1-severe, 2-major (CP)

- *CP = Clinical Pharmacology

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: <https://www-micromedexsolutions-com.libproxy.uthscsa.edu/> (cited: March 27, 2020).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: <http://www.clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/>. Accessed March 27, 2020.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available at <fco-factsandcomparisons-com.ezproxy.lib.utexas.edu>. Accessed March 27, 2020.
4. AHFS Drug Information 2020. Jackson, WY: Teton Data Systems, 2020. Stat!Ref Electronic Medical Library. Available at <online.statref.com.libproxy.uthscsa.edu/>. Accessed March 27, 2020.
5. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020. Available at <online-lexi-com.ezproxy.lib.utexas.edu/lco/action/home>. Accessed March 27, 2020.
6. RED BOOK Online®. In: IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: <https://www-micromedexsolutions-com.libproxy.uthscsa.edu/> (cited: March 27, 2020).
7. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Drugs@FDA. Available at <accessdata.fda.gov/scripts/cder/daf/index.cfm>. March 27, 2020.
8. Chlordiazepoxide package insert. Teva Pharmaceuticals USA, Inc., August 2016.
9. Alprazolam (Xanax®) Package Insert. Pfizer, January 2017.
10. Clobazam (Onfi®) Package Insert. Lundbeck Inc., December 2016.
11. Clobazam oral film (Sympazan®) package insert. Aquestive Therapeutics, Inc., November 2018.
12. Diazepam nasal spray (Valtoco®) package insert. Neurelis, Inc., January 2020.
13. Chlordiazepoxide/amitriptyline (Limbitrol®) package insert. Heritage Pharmaceuticals, Inc., September 2016.
14. Chlordiazepoxide/clidinium (Librax®) package insert. Valeant Pharmaceuticals North America LLC, January 2017.

15. Engorn B, Flerlage J eds. Harriet Lane handbook. 20th ed. Philadelphia: Mosby Elsevier; 2015.
16. Witek MW, Rojas V, Alonso C, Minami H, Silva RR. Review of benzodiazepine use in children and adolescents. *Psychiatr Q.* 2005;76(3):283-96.
17. Kersun LS, Shemesh E. Depression and anxiety in children at the end of life. *Pediatr Clin N Am.* 2007;54:691-708.
18. Cummings MR, Miller BD. Pharmacologic management of behavioral instability in medically ill pediatric patients. *Curr Opin Pediatr.* 2004;16:516-22.
19. Connolly SD, Bernstein GA, and the Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry.* 2007;46(2):267-83.
20. Botts S, Lockwood A, Allen T. Generalized anxiety disorder, panic disorder, and social anxiety disorder. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, et al, eds. *Pharmacotherapy: principles and practice.* 2nd ed. New York: McGraw-Hill; 2010:691-707.
21. Bystritsky A. Pharmacotherapy for generalized anxiety disorder in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 27, 2020.)
22. Leonte KG, Puliafico A, Na P, Rynn MA. Pharmacotherapy for anxiety disorders in children and adolescents. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 27, 2020.)
23. Melton ST, Kirkwood CK. Chapter 87. Anxiety disorders I: generalized anxiety, panic, and social anxiety disorders (Chapter). In: DiPiro JT, Yee GC, Posey LM, et al. *Pharmacotherapy: a pathophysiologic approach.* 11th ed. New York, McGraw-Hill, 2019. Access Pharmacy Web site. Available at accesspharmacy.mhmedical.com.ezproxy.lib.utexas.edu/content.aspx?bookid=1861§ionid=146065193. Accessed March 27, 2020.
24. Katon WJ. Panic disorder. *N Engl J Med.* 2006;354(22):2360-7.
25. Schneier FN. Social anxiety disorder. *N Engl J Med.* 2006;355(10):1029-36.
26. Hoffman EJ, Mathew SJ. Anxiety disorders: a comprehensive review of pharmacotherapies. *Mt. Sanai J Med.* 2008;75:248-62.
27. Work Group on Panic Disorder. American Psychiatric Association Practice Guidelines. Practice guideline for the treatment of patients with panic disorder, second edition. Available at psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf. Accessed March 27, 2020.