

## SEDATIVE-HYPNOTIC AGENTS

### A. FDA approved indications (Documentation Required)

1. Insomnia
2. Sedation for an agitated patient in an inpatient setting
3. EPS (Benadryl)

### B. Non-FDA approved, commonly used indications (Documentation Required)

1. Trazodone
2. Doxepin

For Benzodiazepine non-FDA approved use, please refer to Anti-Anxiety section (Section G).

### C. Minimal documentation

1. All standard outpatient and inpatient requirements
2. For Inpatient: Document rationale when making more than 3 changes in any 7-day period.
3. In patients with substance use, benzodiazepines may be provided in accordance to Section P of medication practice guideline, Guidelines for Prescribing Controlled Psychotropic Medications to Patients with Substance Use.
4. CURES:

Review of cures report is required prior to initiation of any controlled psychotropic medication, and again at intervals no longer than 4 months throughout treatment or whenever misuse of the medications suspected, including when it's used more frequently or at higher dose than prescribed without provider consultation.

### DOCUMENT YOUR OBSERVATION IN THE PROGRESS NOTE.

#### 5. Narcan: (Assembly Bill No. 2760)

- A. When prescribing opioids, the prescriber shall offer a prescription for naloxone to a patient if:
  - The prescription daily dose is >90 morphine mg equivalents
  - An opioid is prescribed with a benzodiazepine
  - The patient has an increased risk of overdose
- B. When prescribing opioids, the prescriber shall provide education on overdose prevention and the use of naloxone to the following individuals:
  - Patient
  - One or more persons designated by the patient

### D. Maximum dosage – see Maximum Daily Dose (MDD); (Documentation Required) Medication Summary (Section B)

### E. Duration (Documentation Required)

1. For Outpatient: Document rationale when making any medication change.
2. Lunesta (eszopiclone) and Rozerem (ramelteon) are the only sedative hypnotic agents approved for insomnia without a specified time limit. The other agents are approved for short term use.

**F. Polypharmacy (Documentation Required)**

1. Prior to consideration of polypharmacy; individual medications should be prescribed at adequate dose, duration and response documented.

2. Polypharmacy (Refer to Purpose Section for exceptions):

The following combinations are considered to be polypharmacy and require the appropriate documentation of rationale including clinical response:

- ≥2 benzodiazepines
- ≥2 non-benzodiazepines
- A benzodiazepine plus a non-benzodiazepine

3. Refer to section E2 for duration of use

**G. Standard laboratory and examination requirements (Documentation Required)**

- Inpatient: Basic laboratory studies on admission

**Drug-Drug Interactions**

Due to the heterogeneity of this class, refer to appropriate references for drug-drug interactions of individual agents.

**H. Black Box Warning**

1. Risks from Concomitant Opioid Use

Concomitant benzodiazepine use with opioids may result in profound sedation, respiratory depression, coma, and death; reserve concomitant use for patient with inadequate alternative treatment options. Limit to minimum required dosage and duration. Monitor patients for signs and symptoms of respiratory depression and sedation.

2. The boxed warning follows several reports of rare, but serious injuries and deaths resulting from various complex sleep behaviors after taking these medicines. These complex sleep behaviors may include sleepwalking, sleep driving and engaging in other activities while not fully awake, such as unsafely using a stove. The new warnings will be required for eszopiclone (Lunesta), zaleplon (Sonata) and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, and Zolpimist). <https://www.fda.gov/news-events/press-announcements/fda-requires-stronger-warnings-about-rare-serious-incidents-related-certain-prescription-insomnia>

**I. Warnings and Precautions (Documentation Required)**

1. Withdrawal reactions/symptoms, such as convulsions, psychosis, rebound anxiety, insomnia, hallucinations, behavioral disorders, tremor, abdominal and muscle cramps, may occur following abrupt discontinuation. The more severe withdrawal symptoms generally occur for those patients receiving higher doses over an extended period of time. However, milder withdrawal symptoms, such as dysphoria and insomnia, have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic doses over several months. Therefore, to minimize discontinuation symptoms after extended exposure, gradual taper from benzodiazepine is recommended.

2. History of alcohol abuse or substance abuse (See Section: P)

3. May cause physical and psychological dependence, tolerance, and withdrawal symptoms

4. Risk of abuse
5. Severe cardiac disease (Chloral Hydrate)
6. Mentally depressed patients
7. Elderly and debilitated patients
8. History of gastritis, esophagitis, or gastric or duodenal ulcers (Chloral Hydrate)
9. Patients with acute or chronic pain (Butisol)
10. Tartrazine (FD&C Yellow No. 5) sensitivity with increase in patients with concomitant aspirin allergy; increased risk of allergic reactions including bronchial asthma in susceptible patients (Butisol in tartrazine preparation, Sonata, Serax)
11. History of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension (Benadryl)
12. Asthma (Atarax, Vistaril)

**J. Drug-Drug Interactions**

Due to the heterogeneity of this class, refer to appropriate references for drug-drug interactions of individual agents.

**K. Adverse Reactions (Document assessment of following)**

**Serious Adverse Reactions**

- Hypersensitivity reaction
- Complex sleep-related behaviors, which may include sleep-driving, making phone calls, and preparing and eating food (while asleep or with no memory of event)
- Impaired mental alertness, next day
- Hallucination
- Amnesia
- Respiratory depression
- Blood dyscrasias
- Dependency, abuse
- Seizure
- Depression/exacerbation/Suicidality
- Bradycardia or tachycardia
- CNS Stimulation, paradoxical
- Withdrawal sx's if abrupt D/C (long-term use)
- Hepatotoxicity
- CNS effects (Cognitive impairment, lack of motor coordination)

**Common Adverse Reactions**

- Headache
- Drowsiness
- Dizziness
- Lethargy
- Drugged feeling
- Diarrhea
- Dysarthria

- Confusion
- Disinhibition
- Abnormal dreams
- Xerostomia
- Venous thrombosis, phlebitis (IM or IV use)
- Nausea/abdominal pain
- Paresthesia

**L. Contraindications (Documentation Required)**

- History of allergy to any drug in the same class
- History of alcohol abuse or substance abuse
- History of addiction
- Sleep Apnea (Dalmane, Doral)
- Severe hepatic impairment (Halcion, Chloral Hydrate, Luminal)
- Severe renal impairment (Chloral Hydrate)
- Severe respiratory disease (Luminal)
- Pregnancy and Nursing Mothers: See Table 2 Pregnancy & Breastfeeding categories
- Newborns or premature infants (Benadryl)
- Narrow angle glaucoma (Ativan, Valium)
- History of manifest or latent porphyria (Barbiturate)

**Major Findings (3/19/14):**

A retrospective cohort study of more than 100,000 age- and sex-matched patients showed that those who used anxiolytics and/or hypnotics were 3 times more likely to die prematurely during the 7-year follow-up period than those who did not use these drugs. The study included benzodiazepines and the “z-drugs” – Zaleplon, zolpidem, and zopiclone. Please refer to large study, published in BMJ in March 19, 2014.

**Attachments:**

Table 1 FDA approved Ind & MDD

Table 2: Pregnancy & breastfeed information

**References:**

- UpToDate: Behavioral and Pharmacological therapies for chronic insomnia in adults:  
<https://www.uptodate.com/contents/behavioral-and-pharmacologic-therapies-for-chronic-insomnia-in-adults>
- Prescriber’s Package Insert for each medication
- Epocrates
- Micromedix
- <http://www.bmj.com/content/348/bmj.g1996#alternate>

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**Table 1: FDA-approved Indications & MDD (DRAFT)**

Generic	Brand	MDD		Insomnia	Sedation	Non-Controlled
		Adult	Children			
<b>Benzodiazepine</b>						
Diazepam	Valium	40mg	10mg (>6mo)		X	
Estazolam	<b>Prosom</b>	2mg	Non-FDA	X		
Flurazepam	<b>Dalmane</b>	30mg	Non-FDA	X		
Lorazepam	Ativan	10mg	4mg (≥12yo)	X		
Oxazepam	Serax	120mg	120mg (≥12yo)			
Quazepam	<b>Doral</b>	30mg	Non-FDA	X		
Temazepam	Restoril	30mg	Non-FDA	X		
Triazolam	Halcion	.5mg	Non FDA	X		
<b>non-Benzodiazepine</b>						
Diphenhydramine	Benadryl	400mg	1mg/kg (2-12yo); 50mg (>12yo)	X		X
Eszopiclone*	<b>Lunesta<sup>1</sup></b>	2mg	Non-FDA	X		
Hydroxyzine	Atarax (HCl), Vistaril (Pamoate)	400mg	50mg (<6yo); 100mg (>6yo)		X	X
Phenobarbital	Luminal	320mg	6mg/kg	X	X	
Ramelteon	<b>Rozerem<sup>1</sup></b>	8mg	Non-FDA	X		X
Secobarbital	Seconal	100mg	5mg/kg or 100mg	X		
Suvorexant	<b>Belsombra</b>	20mg	Non-FDA	X		
Zaleplon	Sonata	20mg	Non-FDA	X		
Zolpidem	Ambien, <b>CR</b>	10mg (CR 12.5)		X		
Zolpidem	<b>Intermezzo<sup>2</sup></b>	Females: 1.75mg SL, Males: 3.5 SL		X		

1. Lunesta (eszopiclone) and Rozerem (ramelteon) are the only sedative hypnotic agents approved for insomnia without a specified time limit. The other agents are approved for **short term use**.
2. For middle-of-the-night waking with difficulty returning to sleep; give only if >4h before planned time of waking; reevaluate if insomnia persists after 7-10 days of tx.

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**Table 2: Pregnancy and Breastfeeding Information (DRAFT)**

<b>Generic</b>	<b>Brand</b>	<b>Pregnancy Information</b>	<b>Breastfeeding Information</b>
<b>Benzodiazepine</b>			
Diazepam	Valium	consider alternative during pregnancy; no human data available; possible risk of teratogenicity based on conflicting animal data at >50x recommended human dose	consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Estazolam	<b>Prosom</b>	avoid use during pregnancy; no human data available, though possible risk of teratogenicity based on conflicting human data w/ other benzodiazepines; risk of floppy infant syndrome near term and neonatal withdrawal sx based on human data w/ other benzodiazepines	use alternative or consider short-acting benzodiazepine while breastfeeding; no human data available to assess risk of infant harm or effects on milk production; possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines
Flurazepam	<b>Dalmane</b>	avoid use during pregnancy; no human data available, though possible risk of teratogenicity based on conflicting human data w/ other benzodiazepines; risk of floppy infant syndrome near term and neonatal withdrawal sx based on human data w/ other benzodiazepines	use alternative or consider short-acting benzodiazepine while breastfeeding; no human data available to assess risk of infant harm or effects on milk production; possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines
Lorazepam	Ativan	weigh risk/benefit in 3rd trimester if prolonged (>3h) or repeated admin. for sedation use, otherwise consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human data and risk of floppy infant syndrome near term based on limited human data; risk of neonatal withdrawal sx based on human data w/ other benzodiazepines; possible risk of teratogenicity based on animal data and risk of embryo-fetal toxicity and death based on animal data w/ PO form at doses of 40 mg/kg; possible risk of adverse neurodevelopmental outcomes based on animal data w/ other sedatives	may use low doses short-term while breastfeeding, otherwise monitor infant closely; no known risk of infant harm based on limited human data, though possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines; no human data available to assess effects on milk production
Oxazepam	Serax	consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human data and risk of neonatal withdrawal sx based on limited human data; risk of floppy infant syndrome near term based on human data w/ other benzodiazepines; no known risk of teratogenicity based on animal data at 100 mg/kg/day	may use low doses short-term while breastfeeding, otherwise monitor infant closely; no known risk of infant harm based on limited human data, though possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines; no human data available to assess effects on milk production
Quazepam	<b>Doral</b>	use alternative during pregnancy; no human data available, though possible risk of teratogenicity based on conflicting human data w/ other benzodiazepines; risk of floppy infant syndrome near term and neonatal withdrawal sx based on human data w/ other benzodiazepines	use alternative or consider short-acting benzodiazepine while breastfeeding; no human data available to assess risk of infant harm or effects on milk production; possible risk of infant CNS depression based on limited human data w/ other benzodiazepines
Temazepam	Restoril	consider alternative during pregnancy; possible risk of teratogenicity based on conflicting human data; risk of neonatal withdrawal sx and floppy infant syndrome near term based on human data w/ other benzodiazepines	may use low doses short-term while breastfeeding, otherwise monitor infant closely; no known risk of infant harm based on limited human data, though possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines; no human data available to assess effects on milk production
Triazolam	Halcion	consider alternative during pregnancy; possible risk of teratogenicity and risk of floppy infant syndrome near term based on limited human data; risk of neonatal withdrawal sx based on human data w/ other benzodiazepines; no known risk of teratogenicity based on animal data at high doses	consider alternative or monitor infant closely while breastfeeding; no human data available to assess risk of infant harm or effects on milk production; possible risk of infant CNS depression based on limited human data w/ longer-acting benzodiazepines

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		<b>Non-Benzodiazepine</b>	
Diphenhydramine	Benadryl	may use during pregnancy; no known risk of fetal harm based on human data	consider alternative, though may use short-term while breastfeeding; possible risk of infant CNS depression based on limited human data; inadequate human data available, though theoretical risk of decr. milk production based on decr. prolactin levels
Eszopiclone	<b>Lunesta</b>	consider alternative during pregnancy; no known risk of teratogenicity based on limited human and animal data; risk of embryo-fetal toxicity based on conflicting animal data at >300x MRHD	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Hydroxyzine	Atarax (HCl), Vistaril (Pamoate)	caution advised during pregnancy; risk of fetal harm low based on limited human data	consider alternative while breastfeeding; possible risk of infant CNS depression based on limited human data; no human data available, though theoretical risk of decr. milk production based on decr. prolactin levels
Phenobarbital	Luminal	weigh risk/benefit during pregnancy; folic acid supplementation recommended in 1st trimester; consider vitamin K administration near term and in neonate; risk of teratogenicity, neonatal vitamin K deficiency-assoc. bleeding, and neonatal withdrawal sx based on human data	consider short-acting barbiturate or monitor infant closely while breastfeeding; risk of infant CNS depression based on limited human data and drug properties; no known adverse effects on milk production based on limited human data
Ramelteon	<b>Rozerem</b>	consider alternative during pregnancy; no human data available; possible risk of teratogenicity based on conflicting animal data at >50x recommended human dose	consider alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Secobarbital	Seconal	consider avoiding use during pregnancy; possible risk of fetal harm based on conflicting human data; possible risk of neonatal withdrawal sx based on drug's mechanism of action	caution advised while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Suvorexant	Belsomra	consider alternative during pregnancy; no human data available; possible risk of decr. fetal wt based on conflicting animal data	use alternative while breastfeeding; no human data available to assess risk of infant harm or effects on milk production
Zaleplon	Sonata	consider alternative during pregnancy; inadequate human data available to assess risk; no known risk of teratogenicity based on animal data at 49x MRHD; risk of embryo-fetal toxicity and death based on animal data at >0.5x MRHD	may use while breastfeeding; no known risk of infant harm based on limited human data and drug properties; no human data available to assess effects on milk production
Zolpidem	Ambien, <b>CR*</b>	consider alternative during pregnancy, esp. during 3rd trimester; no known risk of teratogenicity, though risk of neonatal respiratory depression when given near term based on limited human data; possible risk of embryo-fetal toxicity and death based on animal data at 25x and 125x MRHD	caution advised while breastfeeding; no known risk of infant harm, though possible risk of infant sedation based on limited human data; no human data available to assess effects on milk production

\***Bolded RXs are non-Formulary for SCVH&HS.**