

Sedative/Hypnotics

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MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE

Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with [*].

1.* Dosage

A. Adults

Maximum recommended daily doses for sedative/hypnotics in adults, including the elderly population, are summarized in Table 1. Prescribed dosages exceeding these recommendations will be reviewed.

Table 1
Maximum Recommended Daily Dose for Sedative/Hypnotics in Adults

DRUG	≤ 65 YEARS	> 65 YEARS
<i>Benzodiazepines</i>		
Estazolam (ProSom®)	2 mg	2 mg*
Flurazepam (Dalmane®, generics)	30 mg	15 mg*
Quazepam (Doral®)	30 mg	15 mg*
Temazepam (Restoril®, generics)	30 mg	15 mg*
Triazolam (Halcion®)	0.5 mg	0.25 mg*
<i>Barbiturates</i>		
Butabarbital (Butisol®, generics)	120 mg	120 mg*
Mephobarbital (Mebaral®)	400 mg	400 mg*
Phenobarbital	400 mg	400 mg*
Secobarbital (Seconal®, generics)	200 mg	200 mg*
<i>Miscellaneous Nonbarbiturates</i>		
Chloral hydrate (generics)	oral and rectal: 2000 mg	oral and rectal: 2000 mg
Eszopiclone (Lunesta®)	3 mg	2 mg
Ramelteon (Rozerem®)	8 mg	8 mg
Zaleplon (Sonata®)	20 mg	10 mg
Zolpidem (Ambien®, Ambien CR®)		
immediate-release:	10 mg	5 mg
extended-release:	12.5 mg	6.25 mg

*While the daily dose recorded is the maximum recommended dose assigned to the drug listed, in elderly patients (patients > 65 years of age) sedative/hypnotic dosages should be reduced if possible, as these patients are more sensitive to the pharmacologic effects.

The appropriate sedative/hypnotic dose for debilitated patients is the same as that prescribed in elderly patients for most sedative/hypnotic agents. However, estazolam 0.5 mg is used in small, debilitated patients which is lower than that recommended for elderly patients.

Quazepam dosages for elderly patients should be reduced to the lowest possible dose in one to two days, if possible.

Patients with hepatic insufficiency do not clear zolpidem doses as readily as patients with normal hepatic function. A 5 mg zolpidem immediate-release dose or 6.25 mg extended-release dose is recommended in these patients.

B. Pediatrics

Safety and efficacy of benzodiazepines as sedative/hypnotics, eszoclipone, ramelteon, zaleplon, or zolpidem in pediatric patients have not been established. Chloral hydrate and barbiturates may be used in pediatric patients for short-term management of insomnia (< 2 weeks) and/or to provide sedation prior to nonpainful therapeutic or diagnostic procedures. Dosage recommendations for barbiturates and chloral hydrate for pediatric patients are summarized in Table 2.

Table 2	
Recommended Dosages for Sedative/Hypnotics in Pediatric Patients	
DRUG	RECOMMENDED DOSAGE
<i>Barbiturates</i>	
Butabarbital	Preoperative sedation: 2-6 mg/kg; maximum 100 mg/dose Sedation: 7.5-30 mg orally daily, in divided doses
Mephobarbital (Mebaral®)	Sedation: 16-32 mg orally 3-4 times daily
<i>Miscellaneous Nonbarbiturates</i>	
Chloral hydrate	Insomnia: 50 mg/kg/day; maximum 1 g/dose Procedural Sedation: 25-100 mg/kg/dose orally or rectally; maximum 1 g/dose (infants), 2 g/dose (child) Sedation: 25-50 mg/kg/day orally or rectally, divided every 6-8 hours; maximum 500 mg/dose

2.* Duration of Therapy

In adults, insomnia is classified based on symptom duration. Periods of sleep difficulty lasting from one to three nights are classified as transient insomnia, periods lasting three nights to one month are classified as short-term insomnia, while chronic or long-term insomnia represents sleep difficulties exceeding one month. Acute, transient insomnia is due to minor situational, familial, and/or occupational stress and is managed primarily by teaching patients to re-establish normal sleep-wake patterns. Short-term insomnia is precipitated by events such as divorce, job loss, health concerns, or prescription medications and may be managed by behavioral techniques, lifestyle changes, and, if necessary, short-term pharmacologic therapy. Long-term insomnia may be associated with medical or psychiatric illness (e.g., mood and anxiety disorders, asthma, chronic pain, and gastroesophageal reflux) as well as a variety of prescribed medications, although approximately 50% of patients may develop chronic insomnia due to psychophysiological characteristics. Chronic insomnia with a psychophysiological component is characterized by a marked overconcern about the inability to fall asleep. A definitive diagnosis of the specific cause for long-term insomnia is necessary before a treatment plan can be delineated. Sedative/hypnotics are generally reserved for use in those patients with insomnia in whom secondary causes of insomnia have been evaluated and managed or in whom sleep hygiene practices have failed. Ideally, sedative/hypnotics are not routinely

recommended for the management of chronic insomnia. However, in certain circumstances, these agents may be administered in conjunction with nonpharmacologic therapy in the lowest effective dose several times per week for no more than 1 to 2 months to minimize tolerance and dependence. Chronic insomnia without underlying medical or psychiatric disease can be managed most effectively with a benzodiazepine or nonbenzodiazepine hypnotic used concurrently for a finite time period with daily behavioral therapy. Hypnotics should typically be dosed intermittently once every two to three nights to avoid tolerance and dependence. However, eszopiclone and ramelteon have been approved for use in the long-term management of sleep onset and/or sleep maintenance insomnia, while zolpidem extended-release has been approved for use in managing insomnia without a limit to treatment duration.

Zolpidem immediate-release prescribed quantities should not exceed a one month supply.

Barbiturates are indicated for short-term treatment of insomnia as these agents appear to lose effectiveness in sleep induction and maintenance after 2 weeks.

Sedative/hypnotic treatment regimens lasting longer than four months in adult patients will be reviewed.

In pediatric patients, sedative/hypnotics are primarily used to alleviate anxiety and/or pain associated with painful or nonpainful but threatening procedures. *Due to an increased incidence of deaths associated with chloral hydrate use prior to or following a diagnostic or therapeutic procedure in pediatric patients, the American Academy of Pediatrics recommends that chloral hydrate should only be administered to pediatric patients in a health care facility with close supervision and appropriate monitoring.*

3.* **Duplicative Therapy**

The concurrent use of two or more sedative/hypnotics is not recommended. Additional therapeutic benefit is not appreciated when several sedative/hypnotics are administered in combination. Patient profiles containing concurrent prescriptions for multiple sedative/hypnotics will be reviewed.

The concurrent use of sedative/hypnotics and other sedative/CNS depressant drugs, including antihistamines, other barbiturates, narcotics, anesthetics, and other benzodiazepines, is not recommended.

4. **Drug-Drug Interactions**

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions.

The following drug-drug interactions are considered clinically relevant for sedative/hypnotics. 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:

a. **Barbiturates and Anticoagulants** [*clinical significance level - severe (WebMD); 1 (DIF); 2 (Hansten & Horn)*]

Combined use of barbiturates and anticoagulants such as warfarin results in significant reductions in the hypoprothrombinemic effects of warfarin. Barbiturates induce hepatic microsomal enzymes which causes increased warfarin metabolic clearance. Fatal bleeding episodes have been reported following discontinuation of barbiturate therapy in patients maintained on anticoagulant therapy. Patients receiving barbiturates and anticoagulants concurrently should not discontinue barbiturate therapy abruptly to avoid the risk of significant adverse bleeding effects. Anticoagulant doses will require modification with close monitoring of anticoagulant response if this drug combination is utilized. A benzodiazepine could be considered for use in place of the barbiturate therapy. The combination of barbiturates and anticoagulants should be avoided, if possible. Concurrent use of barbiturates and anticoagulants will be reviewed.

- b. ***Chloral Hydrate and Anticoagulants*** [clinical significance level - severe (WebMD); 3 (DIF); 3 (Hansten & Horn)]

Patients prescribed chloral hydrate concurrently with anticoagulants such as warfarin may experience an enhanced hypoprothrombinemic response to oral anticoagulant therapy. Trichloroacetic acid, a metabolite of chloral hydrate, appears to displace warfarin from its binding sites, resulting in increased free warfarin concentrations. However, these changes appear to be small and transient and do not interfere in overall management of patients maintained on anticoagulants. Patients receiving the chloral hydrate-anticoagulant drug combination should be monitored for enhanced hypoprothrombinemic response during the first few days of chloral hydrate therapy. If desired, benzodiazepines may be substituted for chloral hydrate as these agents have no effect on anticoagulant control.

- c. ***Select Benzodiazepine Hypnotics and Protease Inhibitors (e.g., nelfinavir, ritonavir, saquinavir)*** [clinical significance level - contraindicated (First DataBank); 2 (DIF); 3 (Hansten & Horn)]

Protease inhibitors administered concurrently with certain benzodiazepines may result in enhanced benzodiazepine effects. Protease inhibitors interfere with the cytochrome P450 enzyme system and inhibit hepatic metabolism of those benzodiazepines which undergo oxidative metabolism, such as triazolam. Significant increases in benzodiazepine concentrations may lead to severe sedation and respiratory depression. When adjunctive protease inhibitor and benzodiazepine sedative/hypnotic therapy is necessary, a benzodiazepine metabolized by glucuronidation (e.g., temazepam) may be considered. The combined use of protease inhibitors and those benzodiazepines subject to oxidative metabolism is not recommended and will be reviewed.

- d. ***Select Benzodiazepine Hypnotics and select NNRT Inhibitors [e.g., delavirdine (Rescriptor®), efavirenz (Sustiva®)]*** [clinical significance level - contraindicated (WebMD), 2 (DIF)]

Combined administration of benzodiazepines that undergo oxidative metabolism (e.g., triazolam) and select NNRT inhibitors may result in elevated serum benzodiazepine concentrations and increased risk of toxicity. Delavirdine and efavirenz inhibit CYP3A4, the enzyme responsible for oxidative metabolism of benzodiazepines. Adjunctive use of delavirdine or efavirenz and benzodiazepines subject to oxidative metabolism is not recommended and will be reviewed.

- e. ***Select Benzodiazepine Hypnotics and Triazole (e.g., fluconazole, voriconazole) Antifungal Agents*** [clinical significance level - moderate (WebMD); 3 (Hansten & Horn)]

Adjunctive use of benzodiazepine hypnotics subject to oxidative metabolism with triazole antifungals may result in elevated benzodiazepine serum levels and the potential for enhanced benzodiazepine pharmacologic and adverse effects. Triazole antifungals have been shown to compromise benzodiazepine metabolism by inhibiting CYP3A4 isoenzymes. When concurrent triazole antifungal treatment and benzodiazepine sedative/hypnotic therapy is necessary, a benzodiazepine metabolized by glucuronidation (e.g., temazepam) may be considered.

- f. ***Select Benzodiazepine Sedative/Hypnotics and Macrolides [e.g., erythromycin, clarithromycin (Biaxin®), telithromycin (Ketek®)]*** [clinical significance level – moderate (WebMD); 2 (DIF); 3 (Hansten & Horn)]

Concurrent use of oxidatively metabolized benzodiazepine sedative/hypnotics (e.g., triazolam, estazolam) with macrolide antibiotics such as erythromycin or telithromycin may result in elevated benzodiazepine serum concentrations and enhanced pharmacologic/adverse effects. Select macrolide antibiotics have been shown to delay benzodiazepine sedative/hypnotic metabolism by inhibiting

CYP3A4 isoenzymes, the isoenzymes responsible for benzodiazepine sedative/hypnotic metabolism. When combined macrolide and benzodiazepine sedative/hypnotic therapy is necessary, patients should be monitored for adverse effects and benzodiazepine dosages adjusted as necessary. A benzodiazepine metabolized by glucuronidation (e.g., temazepam) may be an appropriate alternative for patients requiring macrolide antibiotic therapy. **Alternately, azithromycin does not significantly interfere with CYP3A4 metabolism and may be a suitable alternative in patients prescribed sedative/hypnotics requiring macrolide antibiotics.**

g. *Select Benzodiazepine Sedative/Hypnotics and Nefazodone (Serzone®) [clinical significance level - severe (WebMD); 3 (DIF)]*

Combined administration of nefazodone with select benzodiazepine hypnotics that undergo oxidative metabolism may result in elevated serum benzodiazepine concentrations and the potential for enhanced pharmacologic and/or adverse effects. Nefazodone inhibits hepatic metabolism of benzodiazepines subject to oxidative metabolism through competitive inhibition of CYP3A4 isoenzymes. When concurrent nefazodone and benzodiazepine sedative/hypnotic therapy is necessary, patients should be monitored for adverse effects and benzodiazepine dosages adjusted as necessary. A benzodiazepine metabolized by glucuronidation (e.g., temazepam) may be an appropriate alternative for patients requiring nefazodone therapy.

h. *Select Benzodiazepine Sedative/Hypnotics and Imidazole Antifungals (e.g., itraconazole, ketoconazole) [clinical significance level – contraindicated (WebMD); 2 (DIF); 3 (Hansten & Horn)]*

The combined use of itraconazole or ketoconazole and triazolam or estazolam, benzodiazepines that undergo oxidative metabolism, may result in elevated serum benzodiazepine levels and enhanced or prolonged CNS depression. Itraconazole and ketoconazole inhibit metabolism of oxidized benzodiazepines at the cytochrome P450 3A4 isozyme site. Concurrent use of itraconazole or ketoconazole and triazolam or estazolam is contraindicated by the manufacturer and will be reviewed. When adjunctive azole antifungal treatment and benzodiazepine sedative/hypnotic therapy is necessary, a benzodiazepine metabolized by glucuronidation (e.g., temazepam) may be considered.

i. *Long-Acting Barbiturates and Voriconazole (VFend®) [clinical significance level – contraindicated (WebMD); 1(DIF)]*

Long-acting barbiturates may increase triazole antifungal metabolism by inducing CYP3A4 isoenzymes. Consequently, serum concentrations of triazole antifungal agents may be significantly reduced and potentially subtherapeutic. Combined administration of long-acting barbiturates with voriconazole is not recommended by the manufacturer and will be reviewed.

j. *Ramelteon and Triazole (e.g., fluconazole, voriconazole) or Imidazole (e.g., itraconazole, ketoconazole) Antifungal Agents [clinical significance level – unknown]*

Combined administration of ramelteon with either triazole or imidazole antifungal agents may potentially result in increased ramelteon serum concentrations and enhanced pharmacologic and/or adverse effects. Triazole antifungals are potent inhibitors of CYP2C9 while imidazole antifungals significantly inhibit CYP3A4. Patients should be monitored for signs of ramelteon adverse events and adjust drug dosages or discontinue drug therapy as necessary when triazole/imidazole antifungals and ramelteon are administered concurrently.

k. *Ramelteon and Fluvoxamine [clinical significance level – unknown]*

Ramelteon administered concomitantly with fluvoxamine may result in elevated ramelteon serum

concentrations and the potential for enhanced pharmacologic and/or adverse effects. Fluvoxamine is a strong inhibitor of the CYP1A2 isoenzyme. Combined administration of ramelteon with fluvoxamine is not recommended by the manufacturer and will be reviewed.

1. **Barbiturates and Oral Contraceptives** [clinical significance level - severe (WebMD); 1 (DIF); 3 (Hansten & Horn)]

Barbiturates prescribed concurrently with oral contraceptives may result in reduced oral contraceptive effectiveness and the potential for unintended pregnancy. The mechanism by which barbiturates interfere with oral contraceptive efficacy involves induction of contraceptive steroid hepatic metabolism as well as stimulation of sex hormone binding globulin synthesis. Alternative methods of contraception in addition to oral contraceptive use should be considered when barbiturates and oral contraceptives are used adjunctively.

m. **Barbiturates and Cyclosporine** [clinical significance level - severe (WebMD); 4 (DIF); 3 (Hansten & Horn)]

Concurrent administration of barbiturates and cyclosporine may result in reduced cyclosporine effectiveness. Although documentation is limited, enzyme inducers like barbiturates may lower serum cyclosporine concentrations by enhancing hepatic microsomal metabolism of cyclosporine. Barbiturate enzyme-inducing effects are known to have a gradual onset and offset (1 to 2 weeks or more, depending on the barbiturate). Patients receiving cyclosporine therapy should be monitored for changes in clinical response when barbiturate dosages are added, deleted, or modified. Patients maintained on a barbiturate may require higher than anticipated cyclosporine dosages when cyclosporine is added to a previously existing barbiturate dosage regimen.

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