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NEWSLETTER
BENZODIAZEPINE AGENTS
MEDICAID DRUG USE REVIEW CRITERIA FOR OUTPATIENT USE
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BENZODIAZEPINE AGONIST AGENTS

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The benzodiazepines possess at least five properties that make them useful in a variety of disorders: amnesic, anxiolytic, anticonvulsant, muscle relaxant and sedative. The benzodiazepines offer several advantages over other central nervous system depressant drugs including a relatively low incidence of adverse effects, decreased acute toxicity, lower abuse potential and fewer drug interactions.[1-4]

Zaleplon and zolpidem are sedative and hypnotic agents structurally unrelated to the benzodiazepines and other sedative and hypnotic agents. Zaleplon interacts with the GABA-benzodiazepine receptor complex and produces sedative, anxiolytic, anticonvulsive and muscle relaxant effects similar to the benzodiazepines in animal models.[5] Zolpidem does not possess the amnesic, anxiolytic, anticonvulsant or muscle relaxant properties of the benzodiazepines at hypnotic doses.[6,7]

The primary differences among the benzodiazepines are in their pharmacokinetic properties and these are often the main factors affecting drug selection.[1,2,4] See Table 1.

1. **Maximum usual dosage**: Table 2 contains usual dosage ranges and maximum recommended doses for the benzodiazepine agonists. Approximate equivalent doses are presented when available. Doses are those recommended in adults unless otherwise indicated. There is a high degree of interpatient variability in response to the benzodiazepine agonists. The recommended dosage ranges are broad guidelines. In most cases, therapy should be started with the lowest dose and titrated upward until the desired response is achieved. In the treatment of alcohol withdrawal, larger doses are used initially to control symptoms and then tapered as tolerated.[1,2,4,8]

   a. **Dosing in the Elderly.** The capacity for oxidative metabolism decreases with age. The volume of distribution of lipid soluble drugs increases with age. Both effects lead to reduced clearance of benzodiazepine agonists and active metabolites in elderly patients.[1,8] Two of the three benzodiazepines eliminated by conjugation rather than oxidation, lorazepam and oxazepam, do not have significantly longer half-lives in the elderly compared with younger patients.[1,4,10] The half-life of alprazolam, which is also eliminated by conjugation, was increased by approximately 30% in a group of healthy elderly subjects compared with younger adults.[8]

   The pharmacokinetics of zaleplon were not significantly different in a group of elderly subjects compared with young, healthy subjects.[9] Zolpidem's half-life increased by approximately 30% in a group of patients aged 65 to 85, compared with younger patients.[6] Increased pharmacodynamic effects of the benzodiazepines are also seen in the elderly.[4] Recommended starting doses of benzodiazepine agonists for patients over the age of 65 are generally one-third to one-half of those for healthy, younger adults.[1,4,10] Specific

dosage recommendations, where available are included in Table 2.

b. **Tolerance** to the sedative, muscle relaxant and anticonvulsant activities of benzodiazepines develops over time.[1,4] For treatment of seizure disorders, as many as 30% of patients on clonazepam or diazepam demonstrated a loss of efficacy, many within three months. In some cases, dosage adjustment may reestablish seizure control.[8] When used for more than two to four weeks, tolerance to sedative effects has been reported. For benzodiazepines with shorter half-lives, this can result in early morning wakening and increased daytime anxiety or nervousness.[8] The anxiolytic or antipanic efficacies do not appear to decrease over time, although use of benzodiazepines has not been evaluated in long-term trials (greater than four to six months).[1,8] Patients taking benzodiazepines for anxiety or panic disorder, without a history of substance abuse, were unlikely to require increasing doses of benzodiazepines.[2,11]

Reports of tolerance to the effects of zaleplon and zolpidem are mixed. Several reports found no significant development of tolerance with zolpidem when given up to twelve weeks. In the only comparison of zolpidem with a benzodiazepine, both triazolam and zolpidem had similar decreases in sleep versus wake time over the 28-day treatment period.[7]
Zaleplon has not been compared with benzodiazepines, nor has long term use been studied to determine the potential for development of tolerence.[9]

2. **Indication for use:** Benzodiazepines are the drugs of choice for a variety of indications in psychiatric illnesses and other medical disorders. These include treatment of anxiety and panic disorders, muscle spasms, seizures, agitation and insomnia. Their sedative, amnesic and anxiolytic effects also make the benzodiazepines first line agents for conscious sedation.[1-4] The labeled indications for the 14 benzodiazepines currently available in the United States are diverse. These variations in labeled indications generally represent differences in marketing decisions by the manufacturers rather than differences in pharmacological properties of the agents. Differences between the benzodiazepines are also based on their pharmacokinetic profiles. Onset, duration of action, available formulations, and elimination pathways determine suitability of an agent for a particular situation.[2,4]

Zaleplon has anxiolytic, anticonvulsant, and muscle relaxant properties similar to the benzodiazepines in animal models.[5] Information on zaleplon for these indications in humans has not been published. Zolpidem has minimal anxiolytic, amnesic, anticonvulsant or muscle relaxant effects. Both drugs are indicated for the short-term treatment of insomnia.[6,7,12]

3. **Duration of therapy.**

Benzodiazepines are used in a number of chronic illnesses, requiring long-term therapy. There are no standard guidelines for determining duration of therapy with benzodiazepines. Concerns of physiological dependence and abuse potential of the benzodiazepines have led to decreased use of these agents in the past few decades. Many of the conditions treated with benzodiazepines are characterized by subjective symptoms. Recent surveys indicate that attitudes about the conditions being treated and overestimation of the risk for abuse of benzodiazepines have resulted in avoidance of benzodiazepines even in situations where strong evidence is available supporting their efficacy. Prescribers, in many cases, substituted less effective medications with higher potential for toxicity.[2,4] Animal studies used to measure abuse potential of zaleplon, indicated a dependence-producing profile equivalent to benzodiazepines and zolpidem.[5]

a. **Physical dependence** is characterized by physical withdrawal symptoms upon discontinuation. With the benzodiazepines, physical dependence can occur even at low therapeutic doses. The risk of physical dependence increases with dose, duration of treatment, severity of symptoms, use of benzodiazepines with a rapid onset, short duration of action and high potency.[1,2,4] In patients requiring long term therapy with benzodiazepines, use of a long acting

benzodiazepine with a slow onset of action may decrease the risk of dependence and withdrawal.

b. **Withdrawal and rebound** symptoms may occur when benzodiazepines are discontinued. Symptoms of benzodiazepine withdrawal include anxiety, insomnia, tremor, tachycardia, sweating, light sensitivity, depersonalization, distraction, nightmares, hallucinations, and seizures. Withdrawal symptoms refer to those not present prior to benzodiazepine treatment. Rebound symptoms are recurrence of symptoms seen prior to benzodiazepine therapy. Intensity of rebound symptoms is higher than the intensity of original symptoms. The incidence and degree of withdrawal symptoms depend on the duration, dose and half-life of the benzodiazepine. Withdrawal symptoms are more likely with high doses for more than four to six weeks or lower doses for two to four months or longer.[1,4] Onset of withdrawal symptoms for short-acting benzodiazepines occurs within 24 to 48 hours, with peak severity at two to three days after discontinuation. For long-acting benzodiazepines, onset of withdrawal is slower occurring three to seven days after discontinuation.[1,2]

Due to the potential for withdrawal symptoms, it is recommended that benzodiazepines be tapered gradually. Several tapering regimens have been proposed. In general, it is recommended that the dose be tapered by one eighth to one fourth of the original dose every one to two weeks. Within this range, patients on higher doses, shorter acting benzodiazepines should be tapered more slowly. Withdrawal symptoms are more likely towards the end of the taper, so the last weeks of the taper should be more gradual.[1,2,4]

Rebound insomnia was seen with zaleplon during nights one and two after 28-day treatment with zaleplon. Rebound symptoms appeared to be dose related. Withdrawal, defined as three or more new symptoms following discontinuation of zaleplon, was not significantly different from placebo following 14 and 28 days of nightly use.[5,9] Zaleplon has not been directly compared with the benzodiazepines with regard to withdrawal and rebound effects. Animal studies of withdrawal symptoms following discontinuation of zolpidem are mixed. Studies in humans suggest that rebound insomnia occurs following discontinuation of triazolam, but not zolpidem following nightly use. These results have been questioned because the two studies did not use equivalent doses of triazolam and zolpidem. Incidence of physical dependence is dose related.[7]

4. Duplicative therapy.

The benzodiazepine agonists have similar pharmacological effects. Generally, use of two or more benzodiazepine agonists at the same time is not indicated. In rare situations, differences in pharmacokinetic parameters may make use of two agents for different situations in the same patient a reasonable therapeutic choice.

5. Drug-drug interactions

Routine study of drug interactions is a recent requirement in the drug approval process. Information about drug interactions occurring with benzodiazepines is limited to drug interactions expected from basic pharmacokinetics and pharmacology as well as case reports of specific interactions.

Many of the drug interactions seen with the benzodiazepines are due to increases and decreases in hepatic metabolism.[16,17] Benzodiazepine agonists can be divided into two categories based upon the major route of metabolism. Lorazepam, oxazepam and temazepam undergo hepatic glucuronidation. Alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, flurazepam, halazepam, quazepam, midazolam, triazolam, zaleplon, and zolpidem undergo hepatic oxidation via the CYP450 enzyme system. Chlordiazepoxide, diazepam, clorazepate, flurazepam, prazepam, halazepam and quazepam have active metabolites that are also metabolized by this system. Inhibitors, as expected, increase benzodiazepine concentrations and effects. CYP450 enzyme inducers decrease benzodiazepine

concentrations and effects. Most are metabolized primarily by the CYP450 3A isoenzymes, but other subsets are involved to lesser degrees.[14] Those drugs with a high first pass metabolism are most affected be inducers and inhibitors of metabolism. Zaleplon is metabolized by aldehyde oxidase as well as the CYP450 enzyme system. CYP450 enzyme inducers and inhibitors are less likely to alter zaleplon elimination because of this major alternate metabolic pathway.[9,10] The degree of protein binding of the benzodiazepine agonists also influences pharmacokinetic interactions seen with the benzodiazepines. These many variables make accurate prediction of drug interaction outcomes difficult. Since routine testing for and reporting of drug interactions has not been required for the many years most of these agents have been on the market, information on drug interactions with the benzodiazepine agonists is inconsistent and incomplete.[4,13,15,16]

Table 1. Benzodiazepines-pharmacokinetic properties[1,4-6,8,10]

Drug	Onset after oral administration	Protein Binding	Elimination half-life (hours)	Active metabolites*	Major pathway of metabolism	Cytochorme P450 Isoenzymes Involved in Metabolism
Alprazolam	Intermediate	80%	12 to 15	Insignificant	Oxidation	CYP3A3/4
Chlordiazepoxide	Intermediate	90 to 98%	5 to 30	Desmethylchlordiaze-poxide Demoxepam	Oxidation	Not identified
Clonazepam	Fast	85%	18 to 50	Insignificant	Oxidation	CYP3A3/4
Clorazepate Dipotassium	Intermediate	80 to 95%	Not significant	Desmethyldiazepam	Oxidation	CYP2C19
Diazepam	Very fast	98%	20 to 80	Desmethyldiazepam	Oxidation	CYP1A2,2C8, 2C9,2C19 (major) CYP3A3/4 (minor)
Estazolam	Intermediate	93%	10 to 30	Insignificant	Oxidation	Not identified
Flurazepam Hydrochloride	Fast	97%	40 to 114	Desalkylflurazepam	Oxidation	Not identified
Halazepam	Slow		Not significant	Desmethyldiazepam	Oxidation	CYP2C19
Lorazepam	Intermediate	85 to 92%	10 to 20	None	Conjugation	None
Midazolam	Very Fast	95 to 99%	2 to 5	None	Oxidation	CYP3A3/4

Oxazepam	Slow	86 to 96%	5 to 20	None	Conjugation	None
Quazepam	Fast	95 to 99%	25 to 40	2-oxoquazepam, desalkyloxoquazepam	Oxidation	CP4503A, 2C
Temazepam	Intermediate	96%	10 to 20	Insignificant	Conjugation	None
Triazolam	Intermediate	89 to 94%	1.5 to 5	Insignificant	Oxidation	CYP3A3/4, 3A5-7
Zaleplon	Very Fast	60%	1	None	Oxidation	Aldehyde oxidase, CYP3A4
Zolpidem	Fast	92%	2.5	None	Oxidation Hydroxylation	

*The active metabolite desmethyldiazepam has a half-life in adults of 60 to 120 hours, demoxepam 14 to 119 hours, desalkylflurazepam 47 to 100 hours, quazepam's metabolites 40 to 110 hours. This can extend the effects of a benzodiazepine with a relatively short half-life and account for cumulative adverse effects.Table 2. Benzodiazepine agonists - usual and maximum dosage[1,6,8,9,12-15]

Table 2. Benzodiazepine agonists - usual and maximum dosage[1,6,8,9,12-15]

Dosage Form(s)	Drug	Approximate Equivalent Dose	Usual Starting Dose	Usual Maintenance Dose	Maximum Daily Dose	Cost*
Tablets: 0.25mg, 0.5mg, 1mg, 2mg **Oral Concentrate:** 1mg/ml (30mL) **Oral Solution:** 0.5 mg/5mL (500 mL)	**Alprazolam (Xanax®)**	0.5 mg	0.25 to 0.5 mg tid **Elderly patients:** 0.125 to 0.25 mg po bid	0.5 to 4 mg per day. Higher doses may be needed for treatment of panic disorder.	10 mg	$5.81 0.5 mg tid

Capsules: 5mg, 10mg, 25mg **Tablets:** 5mg, 25mg **Powder for injection:** 100mg/ vial	**Chlordiaze-poxide (Librium®)**	10 mg	**Oral:** 5 to 10 mg tid to qid **Elderly patients:** 5 to 10 mg bid **Injectable:** 50 to 100 mg	**Oral:** 5 to 25 mg tid to qid **Elderly oral:** 5 to 10 mg bid to qid **Alcohol withdrawal:** 50 to 100 mg IM or IV (may repeat q 2-4 hours prn **Acute anxiety disorders:** 50 to 100 mg IM or IV, followed by 25 to 50 mg tid to qid **Pre-operative sedation:** 50 to 100 mg IM or IV	300 mg	$4.60 10 mg qid
Tablets: 0.125mg, 0.25mg, 0.5mg, 1mg, 2mg	**Clonazepam (Klonopin®)**	Not available	**Seizures:** 0.5 mg tid **Panic Disorder:** 0.25 mg bid **Infants:** 0.01 mg/kg/day given bid to tid **Children:** 0.03 mg/kg/day given bid to tid	**Adults:** 0.5 to 20 mg/day given bid to tid **Infants and Children:** 0.1 to 0.2 mg/kg/ day given bid to tid	**Seizures**: 20 mg **Panic Disorder:** 4 mg **Infants and Children:** 0.2 mg/kg	$37.31 0.5 mg tid
Tablets: 3.75mg, 7.5mg, 15mg **†SD Tablets:** 11.25mg, 22.5mg	**Clorazepate Dipotassium (Various)**	7.5 mg	7.5 mg tid **Alcohol withdrawal:** 30 mg tid, taper as tolerated **Children 9 to 12 years old:** 7.5 mg bid **Elderly:** 7.5mg bid	15 to 90 mg/day given bid to tid **Children 9 to 12 years old:** 15 to 60 mg/day given bid to tid	90 mg **Children 9 to 12 years old:** 60 mg	$126.49 7.5 mg tid
Tablets: 2mg, 5mg, 10mg **‡Capsules (sustained release):** 15mg **Oral Solution:** 1mg/mL (500mL) **Oral Concentrate:** 5mg/mL **Rectal Gel:** 5mg/mL in 0.5mL, 1mL, 2mL, 3mL, 4mL delivery syringes (2 doses per package) **Injectable solution:** 5mg/mL (1mL, 2mL, 10 mL) **¶Injectable suspension:** 5mg/mL	**Diazepam (Valium®, Diastat®)**	5 mg	**Tablets:** 2 mg bid to qid **Elderly patients:** 2 mg qd to bid **Alcohol withdrawal symptoms:** 10 mg qid **Children over 6 months:** 1 to 2.5 mg tid to qid **Injection:** 2 to 10 mg IM or IV	**Tablets:** 2 to 10 mg tid to qid **Capsules***** **Injection for acute anxiety:** 2 to 10 mg IM or IV repeated every 4 to 6 hours **Injection for status epilepticus:** 5 to 10 mg IV repeated every 10 to 15 minutes up to 30 mg. May repeat in 2 to 4 hours as necessary. Infants over 30 old: 0.2 to 0.5 mg every 2 to 5 minutes up to 5 mg IV. Children over 5 years old: 1 mg every 2 to 5 minutes up to10 mg. **Rectal gel:** mg/kg dose determined dependent upon the patient's age.	Maximum daily dose not defined **Rectal gel** should not be used for more than 5 episodes per month and for no more than 1 episode every 5 days.	$2.51 2 mg qid

Tablets: 1mg, 2mg	**Estazolam (Prosom®)**	1mg	1mg hs **Elderly patients:** 0.5 mg hs	1 to 2 mg po hs	2 mg	$23.50 1 mg hs
Capusles: 15mg, 30mg	**Flurazepam Hydro-chloride (Dalmane®)**	15mg	30 mg hs **Elderly patients:** 15 mg hs	30 mg hs **Elderly patients:** 15 to 30 mg hs	30 mg	$2.03 30 mg hs
Tablets: 20mg, 40mg	**Halezepam (Paxipam®)**	20 mg	20 mg tid to qid	80 to 160 mg per day given tid to qid	160 mg	$63.54 20 mg qid
Tablets: 0.5mg, 1mg, 2mg **Oral solution:** 2mg/mL **Solution for Injection:** 2mg/mL, 4mg/mL	**Lorazepam (Ativan®)**	1 mg	**Oral:** 2 to 3 mg bid to tid **Elderly patients:** 0.5 to 1 mg bid to tid	**Oral:** 1 to 10 mg/day given tid to qid or 2 to 4 mg hs **Injectable (pre-op):** 0.05 mg/kg IM or 0.044 mg/kg IV up to 2 mg **Injectable (status epilepticus):** 0.1 mg/kg (max 4 mg), may repeat in 15 minutes	10 mg	$155.54 3 mg tid
Syrup: 2mg/mL **Solution for Injection:** 1mg/mL, 5mg/mL	**Midazolam (Versed®)**	15 mg (oral)	**Oral as premedication:** 0.15 mg/kg up to 20 mg. **Injectable:** Titrated to effect Loading dose for rapid sedation: 0.01 to 0.05 mg/kg IV	Not applicable	**Oral:** 20 mg **Injectable:** none given	$35.20 1 x 20 mg dose po
Tablets: 15mg **Capsules:** 10mg, 15mg	**Oxazepam (Serax®)**	15 mg	10 mg tid to qid **Elderly:** 10 mg tid **Alcohol withdrawal:** 15 to 30 mg qid	10 to 30 mg tid to qid **Elderly:** 10 to 15 mg tid to qid	120 mg	$30.11 10 mg tid
Tablets: 7.5mg, 15mg	**Quazepam (Doral®)**	15 mg	15 mg hs	7.5 to 15 mg hs	15 mg	$73.92 15 mg hs
Capsules: 7.5mg, 15mg, 30mg	**Temazepam (Restoril®)**	15 mg	15 to 30 mg hs **Elderly:**15mg hs	15 to 30 mg hs **Elderly:** 7.5 to 30 mg hs	30 mg	$7.59 30 mg hs
Tablets: 0.125mg, 0.25mg	**Triazolam (Halcion®)**	0.25 mg	0.25 mg hs **Elderly:** 0.125 mg hs	0.125 to 0.5 mg hs	0.5 mg	$15.86 .25 mg hs
Capsules: 5mg, 10mg.	**Zaleplon (Sonata®)**	NA	10 mg hs **Elderly:** 5 mg hs	5 to 20 mg hs **Elderly:** 5 to 10 mg hs	20 mg	$58.97 10 mg hs

Tablets: 5mg, 10mg.	**Zolpidem (Ambien®)**	15 mg	10 mg hs **Elderly:** 5 mg hs	5 to 10 mg hs **Elderly:** 5 to 10 mg hs	10 mg	$59.22 10 mg hs

†Patients stabilized on clorazepate T-TABS, may be switched to clorazepate SD tablets in the same daily dose given as a single dose every 24 hours.
‡Patients stabilized on doses of 15 mg or more per day may be converted to diazepam sustained release capsules in the same daily dose given every 24 hours.
¶Diazepam emulsion should be administered intravenously only.
* Cost is Medicaid cost for drug only, no dispensing fee, at the maximum Usual Starting Dose