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Drug Class Update: Sedatives

Date of Review: March 2017 **Date of Last Review:** November 2014

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Evidence for the comparative effectiveness of sedatives was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2014. This review examines new comparative evidence of sedatives published since 2014. Though many other sedating medications are often used for sleep disorders, this review will only include medications listed in the Sedative PDL class (see **Appendix 1**). Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants such as trazodone, or atypical antipsychotics. Updates for current sedative prior authorization (PA) criteria are also proposed which restrict use of sedatives to funded conditions, prevent therapeutic duplication, and place quantity limits on sedative use.

Research Questions:
1. Is there any new comparative evidence which assesses efficacy or effectiveness of sedatives (non-benzodiazepine sedatives, benzodiazepine hypnotics, melatonin receptor agonists, orexin receptor antagonists, doxepin, or sedating antihistamines) for treatment of insomnia?
2. Is there new comparative evidence associated with safety of short- or long-term use of sedatives?
3. Are there any subpopulations (specifically elderly and patients with concomitant sleep apnea or mental health disorders) for which sedatives may be more effective or associated with more adverse effects?

Conclusions:
- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents. There is no new evidence for tasimelteon, diphenhydramine, or doxylamine for the treatment of insomnia. Evidence from one systematic review demonstrates similar improvement in total sleep time with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo (standardized mean difference [SMD] 0.44 to 0.64 corresponding to a small to moderate treatment effect).[1] In most cases, sedatives were studied for less than 1 month.[1]
- In the general adult population, total sleep time was improved with short-term use (4-6 weeks) of eszopiclone, zolpidem, suvorexant, and low-dose doxepin compared to placebo (weighted mean difference [MD] of 12 to 48 minutes; moderate quality evidence).[2] There was low quality evidence of no difference in total sleep time with zaleplon compared to placebo.[2]
- Sleep onset latency was also improved in adults taking eszopiclone, zolpidem, ramelteon, suvorexant, and doxepin compared to placebo (weighted MD of 6 to 19 minutes).[2] In the majority of trials the mean sleep latency remained greater than 30 minutes.[2]

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- In elderly patients, there is low quality evidence that eszopiclone improves total sleep time (weighted MD 30 minutes, 95% CI 19.7 to 40.3) and wake time after sleep onset (weighted MD 22 minutes, 95% CI 13.6 to 29.6) compared to placebo.[2] Sleep onset latency is improved with zolpidem (weighted MD 18.3 minutes, 95% CI 5.4 to 31.5) and ramelteon (weighted MD 10 minutes, 95% CI 4.6 to 15.6) compared to placebo (low quality evidence).[2] Evidence from 1 systematic review also supports efficacy of doxepin for the treatment of insomnia in patients over 65 years of age.[3] There is insufficient evidence for other sleep outcomes or treatments.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives. Few randomized control trials (RCTs) for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare.[2] Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia.[2] In addition, the FDA has recently updated warnings for non-benzodiazepine sedatives that emphasize the risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.[4]

Recommendations:
- Streamline and update prior authorization (PA) criteria (see **Appendix 4**) to restrict use of sedatives to OHP-funded conditions, to prevent therapeutic duplication, and to apply quantity limits for all agents in the class.
- Evaluate comparative drug costs in the executive session to inform PDL status.

Previous Conclusions:
- There is no new comparative evidence for newer drugs for insomnia since the literature for this drug class was previously scanned.
- There is no comparative effectiveness or safety evidence for tasimelteon or suvorexant versus other newer drugs for insomnia.
- There is low quality evidence from two small (n= 84, n=20), unpublished, randomized, placebo controlled trials (RCTs) in blind individuals that tasimelteon increases nighttime sleep on the worst 25% of nights by of 50 minutes and decreased daytime sleep on the worst 25% of days by 49 minutes. There is insufficient evidence for adverse drug events of tasimelteon in comparison to placebo.
- There is moderate quality evidence from two, unpublished randomized, placebo-controlled trials that suvorexant statistically significantly increases subjective total sleep time by 10-25 minutes and decreases objective waking after sleep onset by 16 -31 minutes. There is low quality evidence of no significant adverse drug events for suvorexant in comparison to placebo.

Previous Recommendations:
- Make tasimelteon non-preferred due to insufficient evidence for insomnia treatment outside the narrow FDA-approved indication and require a prior authorization for a funded OHP diagnosis.
- Compare costs of suvorexant and other newer drugs for insomnia in the executive session to inform PDL placement.

Background:
Sleep disorders encompass a wide variety of conditions including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.[5] This review will focus primarily on treatment of insomnia and circadian rhythm sleep-wake disorders. Other disorders are discussed only briefly.

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Insomnia is one of the most common sleep disorders. Insomnia is defined as the subjective perception of difficulty with sleep which occurs despite adequate opportunity for sleep and causes functional impairment during the day.[6] Insomnia is often classified as short-term (typically <3 months in duration with an identifiable stressor), long-term (occurring ≥3 times per week for >3 months) or other (if criteria for short- and long-term criteria are not met). Diagnosis is primarily based on sleep history.[5,6] An estimated 30-50% of people experience insomnia symptoms, and insomnia disorder is diagnosed in approximately 4-22% of patients.[7] Insomnia is more common in elderly, females, individuals who are divorced or separated, those with shift work, and patients with lower socioeconomic status.[7] Insomnia symptoms have been associated with reduced health-related quality of life and cognitive decline in patients over 65 years of age.[7] Insomnia can also worsen outcomes for patients with comorbid conditions including cardiovascular disease, post-traumatic stress disorder, and depression.[7] Insomnia may also be associated with a wide variety of conditions, both medical and psychological. Identification and treatment of contributing factors and comorbid conditions (such as medical history, substance misuse and psychiatric conditions) are also important for management of insomnia symptoms.[6] Guidelines from the American Academy of Sleep Medicine for the evaluation and management of chronic insomnia in adults recommend psychological and behavioral treatment as first-line therapies.[6] These approaches may include relaxation therapy, stimulus control therapy, and sleep restriction therapy.[6] Good sleep hygiene is also typically recommended.[6] Pharmacological therapy may be added to behavioral therapy if additional treatment is necessary. Due to a lack of comparative evidence for pharmacological treatment, the American College of Physicians recommends decisions for short-term pharmacotherapy be based on individual risks and benefits of treatment.[8]

Circadian rhythm sleep-wake disorders are associated with a chronic or recurrent pattern of sleep-wake disturbances (> 3 months with the exception of jet lag disorder) and associated daytime distress or impairment.[5] Disorders may be classified as delayed, advanced, irregular, or non-24-hour sleep-wake phase disorders, shift work disorders, jet lag disorders and other disorders.[5] Treatment options recommended for circadian rhythm sleep-wake disorders include melatonin or light therapy.[9,10] Recommendations are also made to avoid sleep-promoting medications in elderly patients with dementia and irregular sleep-wake rhythm disorder based on increased risk of adverse events in this population.[10] Elderly patients, particularly those with baseline cognitive impairment, may be at increased risk for falls, adverse events including confusion and daytime sedation, medication interactions, or drug dependence.[10] No recommendations are made for other treatments due to insufficient evidence.[10]

FDA-approved medications for insomnia include drugs from a wide variety of classes such as benzodiazepines (temazepam, lorazepam, flurazepam, and estazolam), non-benzodiazepine hypnotic sedatives (zolpidem, eszopiclone, or zaleplon), melatonin receptor agonists (ramelteon), orexin receptor antagonists (suvorexant), antihistamines (doxylamine succinate and diphenhydramine) and antidepressants (doxepin).[7] Medications are only indicated for short-term use on an as needed basis but are frequently used routinely long-term. Other medications with sedating properties used off-label for treatment of insomnia include other benzodiazepines (midazolam), sedating antidepressants (trazodone, amitriptyline or mirtazapine) or atypical antipsychotics (quetiapine or olanzapine).[7] Improvement in symptom severity is typically measured by patient-reported improvement in severity, sleep symptoms, and quality of life. However, differences in efficacy are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy. One systematic review examining effect size of the placebo response in RCTs determined that approximately 64% of drug response could be attributed to a placebo effect.[11] Sleep outcomes which are commonly reported in trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Of these outcomes, change in total sleep time is generally considered most clinically significant.[2] However, there is no established consensus on the minimum change in sleep time which correlates with clinical relevance to the patient. Objective assessment of sleep symptoms may also be measured via polysomnography, though subjective assessments may be more relevant to the patient. Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.[2]

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Common adverse effects associated with sedative medications include dizziness, daytime drowsiness, and somnolence. Non-benzodiazepine sedatives have also been associated with infrequent, but serious, adverse effect including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.[12] These warnings are included in the FDA labeling for zolpidem, eszopiclone, zaleplon, and ramelteon.[12] Suvorexant, an orexin receptor antagonist, carries similar warnings in addition to warnings for sleep paralysis, hallucinations, and other neurophychiatric symptoms.[12] Risk for daytime impairment may be higher in women or elderly who eliminate sedative more slowly from the body.[13] The FDA warns that patients with high levels of sedative in the bloodstream can be impaired even if they feel fully awake.[13] For zolpidem in particular, the FDA recommends maximum doses of 5 mg for immediate release products (or 6.25 mg extended release) for women and 10 mg (or 12.5 mg extended release) for men.[13] With long-term use of short- and intermediate-acting sedatives, rebound insomnia has also been noted upon discontinuation of treatment. Sedatives which have been associated with rebound insomnia include zolpidem, eszopiclone, zaleplon, and suvorexant.[14,15] In general, rebound effects were mild and resolved after a few nights.[7]

With the exception of obstructive sleep apnea, medical management of sleep disorders are not funded under the Oregon Health Plan (OHP). Sleep disorders, however, can worsen or exacerbate a funded comorbid condition such as depression or post-traumatic stress disorder (PTSD). In cases such as these, medical management of sleep disorders will be covered. Current policies are in place to restrict use of non-preferred agents to conditions funded by the OHP, to prevent therapeutic duplication of benzodiazepine sedatives, and to limit quantities of benzodiazepine sedatives to no more than 15 doses per 30 days. In quarter 3 of 2016 (July 1 to September 30), 656 patients had claims for sedatives listed in **Appendix 1**. Members with Medicare plans (benefit packages BMM, BMD, MND, or MED) and members with claims due to coordinated care organization (CCO) or Medicare enrollment (explanation of benefits codes 2017, 0154, 1109) were excluded from this population. Details are presented in **Appendix 2**. Immediate-release zolpidem tartrate, a preferred agent available without prior authorization (PA), was the most commonly prescribed sedative accounting for 68% of claims. Because sedatives are indicated for short-term or infrequent use, data were analyzed for the number of prescriptions which had been filled by patients over the course of 3 months. Results are shown in **Table 1**. Data indicates zolpidem was used infrequently for the majority of patients, with 25% (n=111) of patients prescribed less than 15 tablets in 30 days and 45% (n=203) of patients with only 1 claim in the quarter. A handful of patients (n=66) had greater than 3 claims per quarter indicating consistent and regular use of zolpidem.

Table 1. Patients prescribed immediate-release zolpidem tartrate with quantities >15 tablets/30 days.

Number of claims with >15 tablets/30 days	Patients (n=446)
6	1
5	0
4	8
3	57
2	68
1	203
0	109

Other agents commonly prescribed included temazepam (9% of claims) and triazolam (5% of claims). Of the non-preferred agents that required a PA (n=210), 44% (n=92) of claims were approved or a claim for an alternate sedative was received within 90 days of the original sedative claim (defined as the index event). Data were evaluated for potential explanations of patients without a paid claim within 90 days (n=118) of the original sedative claim. For these patients without a paid Medicaid claim within 90 days, 76% (n=90) had been enrolled in a CCO, had lost Medicaid eligibility, or had third-party insurance that may have paid for

the sedative. In 2 cases, the PA had been approved but never filled; and for 26 patients, a PA had never been submitted by the prescriber. Interestingly, upon review of these charts, 9 of these claims were for doxylamine in women with a recent pregnancy diagnosis and 7 claims were for patients on treatment for comorbid depression, bipolar disorder or PTSD. These data indicate that a small population of patients are prescribed zolpidem continuously and implementation of a quantity limit would be feasible. No major safety or access issues were identified.

This review will only include medications listed in the Sedative PDL class (see **Appendix 1**). Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants or atypical antipsychotics. Some of these medications are addressed in other class reviews and are covered with other PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine for insomnia.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
In 2015, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review to examine comparative efficacy of treatments for insomnia disorder in adults.[2] The review included evidence from 38 RCTs which assessed efficacy of pharmacologic interventions for treatment of insomnia.[2] RCTs were required to report sleep outcomes and have at least 4 weeks of follow-up.[2] In many cases, improvement in global sleep outcomes and severity (as measured by the Insomnia Severity Index, the Pittsburgh Sleep Quality Index, or the Patient Global Impression scale) could not be calculated as often trials failed to report baseline global sleep values.[12] Additional sleep outcomes included patient-reported sleep onset latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Overall, most RCTs were limited by small population size, large placebo response, and short duration. Many pharmacological treatments lacked eligible trials.[2] Few trials for benzodiazepines and antidepressants met inclusion criteria, primarily due to short treatment durations and lack of evidence assessing relevant clinical outcomes with these medications.[2] In addition, trials for suvorexant and zolpidem were studied at higher doses than what is now recommended by the FDA.[2] For example, zolpidem 10 to 15 mg was typically used in trials and the FDA recommended dose is now 5 mg.[2] Inclusion of these trials may result in overestimates of treatment effects.

Overall, in short-term placebo-controlled trials, sedative treatment improved sleep symptoms without serious adverse effects.[2] In placebo trials, both eszopiclone and zolpidem demonstrated greater improvements in sleep outcomes than zaleplon.[2] For eszopiclone, approximate change compared to placebo in sleep onset latency, total sleep time, and wake time after sleep onset was 19 minutes (95% CI 14.1 to 24.1), 45 minutes (95% CI 35.4 to 54.2), and 11 minutes (95% CI 1.7 to 19.8), respectively (moderate strength of evidence).[2] In older adults, there was low strength of evidence that eszopiclone improves total sleep time (weighted MD 30 minutes, 95% CI 19.7 to 40.3) and wake time after sleep onset (weighted MD 22 minutes, 95% CI 13.6 to 29.6), but not sleep onset

latency.[2] For zolpidem, approximate sleep onset latency improved by 9-18 minutes and total sleep time improved by 23 to 48 minutes compared to placebo based on moderate strength evidence.[2] Results were similar for all formulations of zolpidem, though no direct comparisons were made.[2] Only extended-release (ER) zolpidem demonstrated an improvement in wake time after sleep onset (weighted MD 16 minutes, 95% CI not reported; low strength of evidence).[2] Similar improvements in sleep onset latency were seen in older adults (weighted MD 18.3 minutes, 95% CI 5.4 to 31.5; n=166; low strength evidence).[2] In adults with insomnia, global outcomes (defined as percentage of patients with a change in the Insomnia Severity Index score >6), were improved with suvorexant 15 to 20 mg compared to placebo (55% vs 42%; RR 1.3, 95% CI 1.2 to 1.5).[12] Sleep onset latency, total sleep time and wake time after sleep onset were also improved with suvorexant compared to placebo by 6 minutes, 16 minutes, and 5 minutes, respectively (moderate quality evidence from 2 RCTs).[12] Ramelteon did not clinically improve global or sleep outcomes compared to placebo in the general adult population (low quality evidence based on 5 RCTs).[2] In older adults, ramelteon improved sleep onset latency by 10 minutes (95% CI 4.6 to 15.6; low quality evidence based on 1 RCT).[12] There was insufficient evidence to demonstrate improvement in sleep latency with zaleplon, and low quality evidence from 2 RCTs demonstrating no difference in total sleep time compared with placebo.[2] There was insufficient evidence to evaluate sleep outcomes with temazepam in the general adult population, but one small study in older adults (n=168) did demonstrate improved sleep onset latency of 20 minutes (95% CI 8.2 to 31.6) compared with placebo (low strength of evidence).[12] Compared to placebo, doxepin 1 to 6 mg improved sleep onset latency an average of 15 minutes, total sleep time by 12-24 minutes, and wake time after sleep onset by 10-17 minutes (low to moderate strength of evidence).[2] However, in the majority of trials which reported improvements in sleep onset latency, the mean sleep onset latency for patients taking non-benzodiazepine sedatives, orexin receptor antagonists and melatonin agonists remained greater than 30 minutes.[12] Direct comparative evidence was limited. Only 4 RCTs compared psychological or behavioral therapy to pharmacologic treatment, and evidence was insufficient to evaluate differences in sleep-related outcomes.[2] One RCT (n=233) did demonstrate greater improvement in total sleep time with zolpidem 10 mg compared to temazepam 20 mg (weighted MD 27 minutes, 95% CI 2.1 to 51.9; low quality evidence).[2] There was insufficient evidence to determine differences in efficacy or safety for other doses, medications, or outcomes.[2] In short-term RCTs, adverse effects of non-benzodiazepine sedatives, ramelteon, suvorexant, and doxepin were not comparably different than placebo.[2] Safety of chronic long-term insomnia treatment in adults was evaluated using 12 observational studies.[2] Trials were limited to studies with a duration of at least 6 months and at least 100 patients without other major comorbid conditions.[2] In general, data indicates that long-term use of sedatives may be associated with increased risk of dementia (4% vs. 1.5%, HR 2.34, 95% CI 1.92 to 2.85).[2] Risks associated with specific medications include an increased risk of head injury or fracture requiring hospitalization with zolpidem (0.60% vs. 0.37%, adjusted HR 1.67, 95% CI, 1.19 to 2.34).[2] Incidence of both dementia and fractures increased in proportion to the dose of sedative prescribed.[2] One large observational study has also associated sedative use with an increased rate of incidental cancers.[2] The study examined incidence of all cancers with the exception of non-melanoma skin cancer. A higher incidence of cancer was associated with patients taking greater than 800 mg/year of zolpidem (HR 1.28, 95% CI 1.03 to 1.59) and greater than 240 mg or 1640 mg per year of temazepam (HR 1.28, 95% CI 1.03 to 1.59 and HR 1.99, 95% CI 1.57 to 2.52, respectively).[2] Two studies which examine effect of sedatives on mortality had inconsistent results.[2] These observational studies were limited by potential unmeasured or unknown confounders, and overall authors rated evidence as insufficient to determine differences in safety between interventions.[2]

Another systematic review of 25 RCTs specifically examined objective sleep outcomes from polysomnographic data.[1] Sedatives included in this review were non-benzodiazepine sedatives (n=851), benzodiazepines (n=152), antidepressants (n=351), and melatonin receptor agonists (n=433).[1] Of the patients included in these trials, 63.2% were female with an average age of 50.5 years (standard deviation [SD] 11.73).[1] Only 7 trials studied durations longer than 1 month, and only 2 studies included participants for longer than 3 months.[1] In order to compare results between classes, effect sizes were calculated using standardized mean differences (SMD) with small, medium, and large effects corresponding to values greater than 0.2, 0.5, and 0.8, respectively.[1] Use of SMD allows for comparisons between multiple evaluation tools and improvement scales. However, correlation of SMD to precise changes in total sleep time or sleep onset latency was not stated. Benzodiazepines, non-benzodiazepine receptor agonists, and antidepressants improved total sleep time by a SMD of 0.64 (95% CI 0.12 to 1.16; p=0.015), 0.52 (95% CI 0.33 to 0.71; p<0.001), and 0.44 (95% CI 0.29 to 0.59; p<0.001), respectively.[1] There was no difference in ramelteon, a melatonin receptor agonist,

compared to placebo in total sleep time.[1] Patients treated with benzodiazepines (SMD -0.76, 95% CI -1.28 to -0.24; p=0.004) and non-benzodiazepine receptor agonists (SMD -0.46, 95% CI -0.61 to -0.31; p<0.001) had a greater change compared to placebo in sleep onset latency than patients on antidepressants (SMD -0.18, 95% CI -0.33 to -0.03, p=0.016).[1] Other sleep outcomes (including wake time after sleep onset and sleep efficacy) for benzodiazepines, non-benzodiazepine receptor agonists, and antidepressants achieved statistical significance with small to medium effect sizes compared to placebo.[1]

The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a rapid response review summarizing efficacy and safety of sedatives for the treatment of insomnia, agitation, or delirium in adults over 65 years of age.[3] The review was limited to data from 3 RCTs that assessed sleep outcomes of doxepin versus placebo.[3] Severity of insomnia was reported using a variety of scales, and in order to compare differences between scales, results were calculated as SMD.[3] SMD evaluates effect sizes on a 0 to 1 scale with effect sizes of 0.2, 0.5 and 0.8 interpreted as small, medium, and large treatment effects.[3] Correlation of SMD to changes in sleep time or quality was not reported. Overall, compared to placebo, doxepin 1 mg, 3 mg, or 6 mg demonstrated a small to medium changes in wake time after sleep onset (SMD range: 0.37 to 0.78), total sleep time (SMD range: 0.33 to 0.97), sleep efficiency (SMD range: 0.41 to 0.98), and sleep quality (SMD: 0.5).[3] No difference was observed in sleep latency or initiation compared to placebo.[3] Authors concluded that doxepin is more effective than placebo for the treatment of insomnia in older adults, though exact correlation to improvements in sleep quality, insomnia severity, or total sleep time were not stated.[3] Rates of adverse events from these 3 RCTs were similar to placebo though evidence was limited by inclusion of a placebo run-in period and lack of reported relevant outcomes.[3]

Discontinuation and taper strategies

The Canadian Agency for Drugs and Technologies in Health (CADTH) completed a systematic review of interventions to promote discontinuation of benzodiazepines and manage withdrawal symptoms associated with discontinuation in patients with a history of long-term benzodiazepine use (>3 months).[4] Evidence from 3 systematic reviews, 5 RCTs, and 3 non-randomized trials were included in the review.[4] Adults in these trials were on average 41 to 79 years of age and were receiving benzodiazepines for a variety of treatments including insomnia, anxiety, panic disorders, or psychiatric disorders.[4] The precise number of patients receiving benzodiazepines for treatment of insomnia was not specified. Interventions included gradual dose-tapering, psychosocial therapy (including cognitive behavioral therapy), patient education, medication substitution, or simple interventions (defined as discontinuation letters from clinicians, self-help information or single consultations with physicians).[4] Most trials examined dose-tapering strategies in combination with nonpharmacological interventions or medication substitution.[4] In many cases, the exact dosing regimen was not specified though some studies used a 25% reduction in dose over 1-4 weeks until drug-free.[4] Due to inadequate reporting, the effectiveness of individual dose-tapering regimens could not be determined, and results of trials were not combined due to large differences in patient populations and interventions.[4] Overall, all nonpharmacological interventions improved the number of patients who successfully discontinued benzodiazepines. Patients who received simple interventions were more likely to successfully discontinue benzodiazepines or reduce benzodiazepine use (RR 2.3, 95% CI 1.3 to 4.2, p=0.008 and RR 2.04, 95% CI 1.5 to 2.8, p<0.001, respectively).[4] Patients who used cognitive behavioral therapy in addition to dose-tapering or supervised withdrawal were more likely to successfully discontinue benzodiazepine use (OR 5.06, 95% CI 2.68 to 9.57, p<0.00001, NNT=3) with reported discontinuation rates of 65 to 85% compared to 25 to 54% in patients with dose-tapering alone.[4] In one RCT, structured educational interventions in conjunction with dose-tapering also improved discontinuation rates compared to usual care (OR 8.3, 95% CI 3.3 to 20.9).[4] Two RCTs examined use of melatonin in combination with dose-tapering without a statistically significant benefit compared to placebo.[4] Other observational studies evaluated use of pregabalin, hydroxyzine, or valerian as adjuvant treatment to tapering regimens, but quality of evidence was limited.[4] The evidence was further limited by patients included in these trials. In several RCTs, a large percentage of eligible patients (66-82%) declined to participate, limiting generalizability of these findings.[4]

Another systematic review, examining the effect of melatonin on discontinuation of benzodiazepines in adults, had similar findings as the previous review with no difference in discontinuation rates when melatonin 2-5 mg daily was used in combination with tapering strategies.[16] Six RCTs (n=332) examining benzodiazepines were included in the review.[16] One trial also included patients on zolpidem or zopiclone.[16] Tapering regimens varied between studies with total durations of 4 to 10 weeks.[16] Doses were typically decreased weekly or every 2 weeks by 25 to 50%.[16] Overall, there was no difference in discontinuation rates in patients taking melatonin versus placebo (OR 0.72, 95% CI 0.21 to 2.41, p=0.59).[16] Changes in sleep quality were reported in 4 trials, but pooled results were not calculated due to significant heterogeneity between studies.[16] Results were inconsistent, with 2 RCTs reporting improved sleep quality with melatonin and 2 trials reporting no difference in sleep quality compared to placebo.[16]

A systematic review by CADTH in 2015 examining discontinuation strategies of non-benzodiazepine sedative hypnotics including zolpidem, eszopiclone, zopiclone and zaleplon identified no additional systematic reviews or RCTs.[17]

New Guidelines:

In 2016, the American College of Physicians updated guidelines for treatment of insomnia based on evidence from the recent systematic review by AHRQ.[8] Recommended first-line therapy is cognitive behavioral therapy for insomnia (CBT-I; strong recommendation based on moderate quality evidence).[8] CBT-I consists of a combination of behavioral interventions such as sleep restriction, stimulus control, and education concerning good sleep hygiene.[8] Second-line therapy for insomnia includes pharmacological therapy. Guidelines recommend using an individualized evaluation of risks and benefits to decide whether to add pharmacological therapy in adults for which CBT-I was unsuccessful (weak recommendation based on low quality evidence).[8] Overall, authors determined that there was insufficient evidence to examine comparative efficacy of pharmacological treatments for insomnia.[8] In the general adult population, eszopiclone, zolpidem, suvorexant, and doxepin improved sleep outcomes compared to placebo.[8] These medications also improve sleep outcomes in adults greater than 55 years of age.[8] In one trial, ramelteon also demonstrated reduced sleep onset latency in older adults.[8] In general, evidence for these pharmacological treatments was of low to moderate quality. Evidence for other treatments including benzodiazepines was insufficient.[8] Data from observational studies indicates that sedative use may be associated with increased risk for dementia and fractures.[8] Post-marketing data also indicates that sedatives may be associated with rare but serious adverse effects such as cognitive and behavioral changes, driving impairment, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.[8] To minimize the risk for these adverse effects, the FDA recommends short-term use (maximum 4 to 5 weeks) of sedatives and lower doses of sedatives in women and older or debilitated adults.[8] There is insufficient evidence regarding long-term use of sedatives, and the FDA recommends further evaluation for patients whose symptoms do not improve within 7 to 10 days of treatment.[8]

In 2015, the American Academy of Sleep Medicine published updated guidelines for the treatment of intrinsic circadian rhythm sleep-wake disorders.[10] The guideline covers advanced and delayed sleep-wake phase disorders as well as non-24-hour and irregular sleep-wake rhythm disorders.[10] Trials were included in the systematic review if they describe symptoms consistent with a circadian rhythm sleep-wake disorder, even if diagnostic criteria were not strictly defined.[10] Therefore, patients with varied descriptions of insomnia, nighttime wakefulness, and daytime functional impairment were included in the review.[10] Overall, evidence for use of sedatives was insufficient to make recommendations for the majority of these disorders.[10] Pharmacological recommendations include the use of strategically timed melatonin in delayed sleep-wake phase disorder (weak recommendation) and non-24-hour sleep-wake rhythm disorder in blind adults (weak recommendation).[10] There is some evidence for use of melatonin in children or adolescents with irregular sleep-wake rhythm disorders (weak recommendation).[10] Sedatives are not recommended in elderly patients with irregular sleep-wake rhythm disorders (strong recommendation), and clinicians should avoid use of melatonin in older patients with dementia for irregular sleep-wake rhythm disorders (weak recommendation).[10] The recommendation to avoid sedatives or hypnotics in older patients is based primarily on the lack of evidence supporting efficacy for these sleep disorders and the high risk for adverse effects, especially in an elderly patients with dementia.[10] The recommendation includes use of off-label antidepressants and antihistamines for sleep disorders.[10]

Evidence supporting efficacy of trazodone in irregular sleep-wake rhythm disorder is limited, and use can be associated with adverse effects of priapism, orthostatic hypotension and cardiac arrhythmias.[10] Adverse effects associated with antihistamines include anticholinergic responses, daytime somnolence and cognitive impairment.[10]

Updates from the American Geriatrics Society for potentially inappropriate medication use in older adults make similar recommendations for sedative use in elderly patients.[18] Benzodiazepines (both short- and long-acting), non-benzodiazepine hypnotics without consideration of duration (eszopiclone, zolpidem, and zaleplon), high-dose doxepin (dose >6 mg/day) and antihistamines with anticholinergic properties (diphenhydramine and doxylamine) should be avoided in adults greater than 65 years of age due increased risk of adverse effects (strong recommendation with moderate quality evidence).[18] These medications may be appropriate for some circumstances and conditions, but evidence for efficacy in adults over 65 years of age for treatment of insomnia is limited.[18] Recommendations are also made to avoid use of these medications in patients with delirium (strong recommendation, moderate quality evidence), dementia or cognitive impairment (strong recommendation, moderate quality evidence), or history of falls or fractures (strong recommendation, high quality evidence).[18]

New Formulations or Indications:
No new formulations or indications were identified.

New FDA Safety Alerts:
In 2016, safety labeling for temazepam was updated to include a boxed warning describing risks from use with concomitant opioids.[13] Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.[13] Recommendations are made to reserve concomitant prescribing to patients for which alternate treatments are inadequate, limit dosage and duration to minimum amounts required, and monitor patients for respiratory depression and sedation.[13]

In 2016, safety labeling for zolpidem tartrate and zolpidem ER was updated to include a warning for hepatic encephalopathy in patients with hepatic insufficiency.[13] Patients with hepatic insufficiency do not clear zolpidem tartrate as rapidly and use in patients with severe hepatic impairment should be avoided.[13] In addition, warnings were updated to emphasize risk for central nervous system depression and next-day impairment, including drowsiness, prolonged reaction time, sleepiness, blurred or double vision, and impaired driving. In order to minimize risk, 7-8 hours of sleep is recommended.[13]

Randomized Controlled Trials:
A total of 156 citations were manually reviewed from the initial literature search. Only trials reporting new comparative evidence were considered for inclusion. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

Route	Formulation	BRAND	GENERIC	PDL
ORAL	TABLET	AMBIEN	ZOLPIDEM TARTRATE	Y
ORAL	TABLET	ZOLPIDEM TARTRATE	ZOLPIDEM TARTRATE	Y
ORAL	CAPSULE	HETLIOZ	TASIMELTEON	N
ORAL	CAPSULE	SONATA	ZALEPLON	N
ORAL	CAPSULE	ZALEPLON	ZALEPLON	N
ORAL	CAPSULE	Z-SLEEP	DIPHENHYDRAMINE HCL	N
ORAL	LIQUID	SLEEP TIME	DIPHENHYDRAMINE HCL	N
ORAL	SPRAY/PUMP	ZOLPIMIST	ZOLPIDEM TARTRATE	N
ORAL	SYRUP	MIDAZOLAM HCL	MIDAZOLAM HCL	N
ORAL	TAB MPHASE	AMBIEN CR	ZOLPIDEM TARTRATE	N
ORAL	TAB MPHASE	ZOLPIDEM TARTRATE ER	ZOLPIDEM TARTRATE	N
ORAL	TABLET	BELSOMRA	SUVOREXANT	N
ORAL	TABLET	ESZOPICLONE	ESZOPICLONE	N
ORAL	TABLET	LUNESTA	ESZOPICLONE	N
ORAL	TABLET	NIGHTTIME SLEEP AID	DIPHENHYDRAMINE HCL	N
ORAL	TABLET	ROZEREM	RAMELTEON	N
ORAL	TABLET	SILENOR	DOXEPIN HCL	N
ORAL	TABLET	SLEEP AID	DIPHENHYDRAMINE HCL	N
ORAL	TABLET	SLEEP AID	DOXYLAMINE SUCCINATE	N
ORAL	TABLET	SLEEP TABS	DIPHENHYDRAMINE HCL	N
SUBLINGUAL	TAB SUBL	EDLUAR	ZOLPIDEM TARTRATE	N
SUBLINGUAL	TAB SUBL	INTERMEZZO	ZOLPIDEM TARTRATE	N
SUBLINGUAL	TAB SUBL	ZOLPIDEM TARTRATE	ZOLPIDEM TARTRATE	N
ORAL	CAPSULE	FLURAZEPAM HCL	FLURAZEPAM HCL	
ORAL	CAPSULE	RESTORIL	TEMAZEPAM	
ORAL	CAPSULE	TEMAZEPAM	TEMAZEPAM	
ORAL	SYRUP	MIDAZOLAM HCL	MIDAZOLAM HCL	
ORAL	TABLET	ESTAZOLAM	ESTAZOLAM	
ORAL	TABLET	HALCION	TRIAZOLAM	
ORAL	TABLET	TRIAZOLAM	TRIAZOLAM	

Appendix 2. Drug Use Data for Sedatives from July through September 2016

	Initially Paid		Paid Within 30 days		Paid Within 31-90 Days		Another Drug in PDL Class Paid Within 30 days		Another Drug in PDL Class Paid Within 31-90 days		No Drugs Within PDL Class Paid Within 90 Days		Total #	Total %
Row Labels	#	%	#	%	#	%	#	%	#	%	#	%		
Sedatives	514	78%	10	2%	2	0%	9	1%	3	0%	118	18%	656	100%
Null	48	51%	0	0%	0	0%	6	6%	2	2%	39	41%	95	100%
MIDAZOLAM HCL	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%
TEMAZEPAM	16	28%	0	0%	0	0%	6	10%	2	3%	34	59%	58	100%
TRIAZOLAM	31	86%	0	0%	0	0%	0	0%	0	0%	5	14%	36	100%
Y	443	99%	2	0%	1	0%	0	0%	0	0%	0	0%	446	100%
ZOLPIDEM TARTRATE	443	99%	2	0%	1	0%	0	0%	0	0%	0	0%	446	100%
N	23	20%	8	7%	1	1%	3	3%	1	1%	79	69%	115	100%
BELSOMRA	2	67%	0	0%	0	0%	0	0%	0	0%	1	33%	3	100%
ESZOPICLONE	8	32%	1	4%	1	4%	2	8%	0	0%	13	52%	25	100%
ROZEREM	3	21%	2	14%	0	0%	0	0%	0	0%	9	64%	14	100%
SILENOR	0	0%	0	0%	0	0%	0	0%	0	0%	2	100%	2	100%
SLEEP AID	0	0%	0	0%	0	0%	0	0%	0	0%	15	100%	15	100%
UNISOM SLEEP AID	0	0%	0	0%	0	0%	0	0%	0	0%	5	100%	5	100%
ZALEPLON	3	14%	3	14%	0	0%	1	5%	0	0%	15	68%	22	100%
ZOLPIDEM TARTRATE ER	7	27%	2	8%	0	0%	0	0%	0	0%	17	65%	26	100%
WAL-SOM	0	0%	0	0%	0	0%	0	0%	1	33%	2	67%	3	100%
Grand Total	**514**	**78%**	**10**	**2%**	**2**	**0%**	**9**	**1%**	**3**	**0%**	**118**	**18%**	**656**	**100%**

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Row Labels	Enrolled in CCO		Lost Eligibility		Has Other Insurance		Indian Health Service Coverage		PA Approved		PA Not Requested		Total #	Total %
	#	%	#	%	#	%	#	%	#	%	#	%		
Sedatives	44	37%	14	12%	24	20%	8	7%	2	2%	26	22%	118	100%
Null	18	46%	4	10%	9	23%	1	3%	0	0%	7	18%	39	100%
TEMAZEPAM	17	50%	4	12%	6	18%	1	3%	0	0%	6	18%	34	100%
TRIAZOLAM	1	20%	0	0%	3	60%	0	0%	0	0%	1	20%	5	100%
N	26	33%	10	13%	15	19%	7	9%	2	3%	19	24%	79	100%
BELSOMRA	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%	1	100%
ESZOPICLONE	7	54%	2	15%	3	23%	0	0%	0	0%	1	8%	13	100%
ROZEREM	4	44%	1	11%	0	0%	1	11%	1	11%	2	22%	9	100%
SILENOR	1	50%	0	0%	0	0%	0	0%	1	50%	0	0%	2	100%
SLEEP AID	2	13%	0	0%	0	0%	6	40%	0	0%	7	47%	15	100%
UNISOM SLEEP AID	1	20%	0	0%	2	40%	0	0%	0	0%	2	40%	5	100%
ZALEPLON	2	13%	2	13%	5	33%	0	0%	0	0%	6	40%	15	100%
ZOLPIDEM TARTRATE ER	7	41%	5	29%	5	29%	0	0%	0	0%	0	0%	17	100%
WAL-SOM	1	50%	0	0%	0	0%	0	0%	0	0%	1	50%	2	100%
Grand Total	**44**	**37%**	**14**	**12%**	**24**	**20%**	**8**	**7%**	**2**	**2%**	**26**	**22%**	**118**	**100%**

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to December Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 09, 2016

1	exp Sleep Wake Disorders/	77864
2	exp "hypnotics and sedatives"/ or exp diazepam/ or exp lorazepam/ or exp midazolam/ or exp trazodone/ or exp quetiapine fumarate/	120719
3	zolpidem.mp.	2355
4	zaleplon.mp.	366
5	exp Sleep Aids, Pharmaceutical/	6649
6	exp Orexin Receptor Antagonists/ or suvorexant.mp.	264
7	ramelteon.mp. or exp Melatonin/	18003
8	tasimelteon.mp.	55
9	exp Doxylamine/	376
10	exp Temazepam/	676
11	exp Triazolam/	1261
12	exp Estazolam/	104
13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	142189
14	1 and 13	5687
15	limit 14 to (english language and humans and yr="2014 -Current")	475
16	limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	156

Sedatives

Goal(s):

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent duplicate use of sedatives.
- Restrict long-term sedative use to due to insufficient evidence and to limit adverse effects. “Grandfather” patients coming into the OHP fee-for-service plan already on chronic sedative use (use for >90 days).

Length of Authorization:

Up to 12 months (criteria specific)

Requires PA:

- Non-preferred sedatives
- All sedatives that exceed 15 doses per 30 days
- Concomitant use of more than one benzodiazepine, more than one non-benzodiazepine sedative, or the combination of a benzodiazepine and non-benzodiazepine sedative in the prior 30 days.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #3
3. Does patient have diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr><td>4. Is patient on CPAP?</td><td>Yes: Approve for up to 12 months.</td><td>No: Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics, due to depressant effect, are contraindicated.</td></tr>
<tr><td>5. Is the patient being treated for co-morbid:
Depression;
Anxiety or panic disorder; or
Bipolar disorder?
AND

Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?</td><td>Yes: Approve for up to 12 months</td><td>No: Pass to RPh; Go to #6</td></tr>
<tr><td>6. Is this request for zolpidem below the maximum daily recommended FDA dose?

<table><tr><th></th><th>Immediate Release</th><th>Extended Release</th></tr><tr><td>Females</td><td>5 mg daily</td><td>6.25 mg daily</td></tr><tr><td>Males</td><td>10 mg daily</td><td>12.5 mg daily</td></tr></table></td><td>Yes: Go to #7</td><td>No: Pass to RPh. Deny; medical appropriateness.</td></tr>
<tr><td>7. Has the patient been treated with a non-benzodiazepine sedative or benzodiazepine hypnotic within the past 30 days?</td><td>Yes: Go to #8</td><td>No: Go to #9</td></tr>
<tr><td>8. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?</td><td>Yes: Document reason for switch and approve duplication for 30 days.</td><td>No: Pass to RPh. Deny; medical appropriateness. There is no evidence to support the concomitant use of two different sedatives.</td></tr>
</table>

Approval Criteria		
9. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #10
10. RPh only: Is this a request for continuation therapy for a patient with a history of chronic use where discontinuation would be difficult or unadvisable? NOTE: New patients on the OHP FFS plan already on chronic sedative are "grandfathered."	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *3/17 (SS); 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *TBD; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Non-Benzodiazepine Sedatives

Goal(s):

- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is.
- Prevent adverse events associated with long-term sedative use. Clients coming onto the plan on chronic sedative therapy (continuously for >90) are "grandfathered." (Refer to criteria).
- See related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature. There is a documented increased risk of serious adverse events in the elderly.

Length of Authorization:

6 months to 12 months (criteria specific)

Requires PA:

- Non-preferred sedatives

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does client have diagnosis of insomnia with sleep apnea?	Yes: Go to #3.	No: Go to #4.
3. Is client on CPAP?	Yes: Approve for up to 1 year. The use of CPAP essentially negates the sedative contraindication and they are often prescribed to help clients cope with the mask.	No: Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics, due to depressant effect, are contraindicated for this diagnosis and are not approvable.

Approval Criteria		
4. Is the client being treated for: • Co-morbid depression, • Anxiety, • Bipolar disorder or • Panic (i.e. Is there an existing claim history of: • Antidepressants, • Lithium, • Antipsychotics, or • Other appropriate mental health drugs)?	Yes: Approve for up to 1 year	No: Pass to RPh. Go to #5.
5. RPh only: Is diagnosis being treated a funded condition on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to see if they are funded or not.	Funded: Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	Not Funded: Go to #6.
6. RPH only: Is this a request for continuation therapy for client with history of chronic use where discontinuation would be difficult or unadvisable? NOTE: Clients coming onto the plan on chronic sedative therapy are “grandfathered.”	Yes: Document length of treatment and last follow-up date. Approve for up to 1 year.	No: Deny; medical appropriateness

P&T/DUR Review: *11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Sedatives – Quantity Limit

Goal(s):

- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not funded, but insomnia contributing to covered comorbid conditions is.
- Prevent adverse events associated with long-term sedative use.
- Clients coming onto the plan on chronic sedative therapy are grandfathered (refer to criteria). Also see related Sedative Therapy Duplication edit. The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

6 to 12 months (criteria specific)

Requires PA:

- All CNS sedatives in Standard Therapeutic Class 47 that exceed 15 doses per 30 days.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does client have diagnosis of insomnia with sleep apnea?	Yes: Go to #3.	No: Go to #4.
3. Is client on CPAP?	Yes: Approve for up to 1 year. The use of CPAP essentially negates the sedative contraindication and they are often prescribed to help clients cope with the mask.	No: Pass to RPh. Deny; medical appropriateness. Due to the depressant effects of sedative/ hypnotics, sedative/hypnotics are contraindicated for this diagnosis and are not approvable.

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Approval Criteria		
4. Is the client being treated for co-morbid depression, bipolar disorder; OR Panic disorder; AND Is there an existing claim history of antidepressants, lithium, antipsychotics, or other appropriate mental health drugs?	Yes: Approve for up to 1 year.	No: Pass to RPh. Go to #5.
5. RPh only: Is diagnosis being treated a covered indication on the OHP and is there medical evidence of benefit of the prescribed sedative? All indications need to be evaluated as to whether they are funded or not.	Funded: Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	Not Funded: Go to #6.
6. RPh only: Is this a request for continuation therapy for client with history of chronic use where discontinuation would be difficult or unadvisable? NOTE: Clients coming onto the plan on chronic sedative therapy are "grandfathered."	Yes: Document length of treatment and last follow-up date. Approve for up to 1 year.	No: Deny; medical appropriateness

P&T/DUR Review: *3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *7/1/14, 1/1/07, 7/1/06, 11/15/05*

Sedatives – Therapeutic Duplication

Goal(s):

- Prevent duplicate sedative use.
- Approve only for OHP-funded conditions.
- Treatment of uncomplicated insomnia is not covered; insomnia contributing to covered comorbid conditions is.
- Also see related Benzo Quantity edit and Non-benzo Sedative edit.
- The safety and effectiveness of chronic sedative use is not established in the medical literature.

Length of Authorization:

1 month

Requires PA:

- Concurrent therapy with more than one sedative drug in Class 47.
- The plan prohibits the client from receiving two oral sedative medications at the same time. POS system screens duplicate oral sedative claims in the prior 30 days. If client has a covered diagnosis, treatment with any single agent is approvable.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record the diagnosis, ICD10 code and reject the internal error code.	
2. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	Yes: Document reason for switch and approve duplication for 30 days.	No: Pass to RPh. Deny; medical appropriateness. There is no evidence to support the use of two different sedatives concurrently. Continuous use of a single sedative is approvable for covered diagnoses. (See benzo quantity limit sedative and non-benzo PA)

P&T/DUR Review: *5/18/06*
Implementation: *7/1/14*