Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review: Circadian Rhythm Sleep Disorders

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Purpose for Class Review:
To evaluate efficacy and safety of medications, including stimulants and sedating drugs, for circadian rhythm sleep disorders.

Plain Language Summary:

- People have difficulty sleeping during the night and staying awake during the day when their body's internal sleep cycle does not match their usual sleep schedule. These specific types of sleep problems are called circadian rhythm sleep-wake disorders. Examples include shift work disorder and jet lag.
- Evidence shows 2 types of medicines may help people with these types of sleep disorders:
    - Sedative medicines that help people sleep better during the night or
    - Stimulant medicines like armodafinil, modafinil, and caffeine that help people stay awake longer during the day.
- Researchers have not studied other stimulants in people with circadian rhythm sleep disorders.
- Changes in lifestyle may improve sleep problems for people with these conditions. For example, people may be more alert during the day and get better sleep when they:
    - change their exposure to bright light,
    - change the time of day that they exercise,
    - change their bedtime, or
    - plan naps during the day.
- To improve sleep, the American Academy of Sleep Medicine recommends melatonin and medicines that act like melatonin in the body for:
    - adults who are blind,
    - people who have difficulty falling asleep at night, and
    - children with conditions affecting their brain development.
- In people who have trouble staying awake at work, armodafinil and modafinil may help people avoid error during work, but they also have serious side effects including risk for heart problems, thoughts of suicide, and skin damage.
- In people who have trouble falling asleep after working a night shift, melatonin may help people sleep about 15 to 30 minutes longer compared to no treatment.
- Evidence does not show that any one medicine is better than another, or that medicine is better than lifestyle changes.
- Providers must explain to the Oregon Health Authority why someone needs a sedative or stimulant before Medicaid will pay for it. This process is called prior authorization.

Author: Sarah Servid, PharmD

- Medicaid Open Card will pay for caffeine tablets when prescribed by a provider without prior authorization. Medicaid Open Card will pay for melatonin without prior authorization when prescribed for children. Melatonin is not covered for adults.
- We recommend Medicaid continue to pay for medicines for circadian rhythm sleep-wake disorders only when necessary, on a case-by-case basis.

Research Questions:

1. What is the comparative efficacy or effectiveness of drugs (e.g., sedative hypnotics, melatonin, melatonin agonists, benzodiazepines, or stimulants) for treatment of circadian rhythm sleep-wake disorders?
2. What is the comparative safety of drugs for treatment of circadian rhythm sleep-wake disorders?
3. Are there any subpopulations who would receive more benefit or suffer more harm from drugs for treatment of circadian rhythm sleep-wake disorders (e.g., based on disease severity markers, specific types of circadian rhythm sleep-wake disorders, or comorbid conditions)?

Conclusions:

- There is insufficient direct evidence to evaluate comparative efficacy or safety of stimulants or sedatives for circadian rhythm sleep-wake disorders.
- There is insufficient evidence to support use of sedative hypnotics (e.g., zolpidem, eszopiclone, zaleplon, orexin receptor antagonists, or benzodiazepines) in people with circadian rhythm sleep-wake disorders.[1,2]
- Stimulants which have been studied for circadian rhythm sleep-wake disorders include modafinil, armodafinil, and caffeine. There is no evidence to support use of other stimulants for treatment of circadian rhythm sleep-wake disorders.
- There are no drugs currently approved by the Food and Drug Administration (FDA) for treatment of jet lag. A recent systematic review found insufficient evidence for use of pharmacologic treatments (including stimulants, sedative hypnotics, melatonin or melatonin agonists) for athletes with jet lag.[3]
- In patients with shift work disorder, melatonin and stimulants have the most evidence for use. In people with shift work disorder, there is insufficient evidence comparing efficacy or safety of melatonin, modafinil, armodafinil, and caffeine.
    - Evidence supporting efficacy of melatonin for shift work disorder is mixed. There is low quality evidence that melatonin may increase self-reported total sleep time by less than 30 minutes within 24 hours after administration in people with shift work disorder, but the clinical significance of this difference is unclear.[1] The only study which evaluated objective sleep time did not identify any differences between melatonin and placebo, and there is low quality evidence of no difference in sleep latency or sleep quality compared to placebo. [1]
    - In adults with shift work disorder and symptoms of moderate to severe excessive sleepiness, modafinil and armodafinil decreased sleepiness during the night shift (mean difference of about one point on the 9-point Karolinska Sleepiness Scale [KSS]), but was associated with more serious adverse events (9.7% vs. 2.4%; relative risk [RR] 3.97; 95% Confidence Interval [CI] 1.15 to 13.71).[1] Latency to persistent sleep during the work shift was improved by an average of 1-3 minutes compared to placebo, and remained less than 6 minutes for most patients indicating continued moderate to severe sleepiness.[4,5]
    - In shift work disorder, a 2010 Cochrane review found low quality evidence that caffeine may reduce errors at work, but there was insufficient evidence for the prevention of injuries during work.[6]
- Systematic reviews evaluating use of melatonin for sleep disorders in people who are blind have found insufficient evidence for efficacy and safety of melatonin.[7,8]
- Guidelines from the American Academy of Sleep Medicine (2015) recommend melatonin or a melatonin agonist for the following intrinsic circadian rhythm sleep-wake disorders: [2]
    - Adults, adolescents, and children with delayed sleep-wake phase disorder (low to moderate quality evidence).

- Adults who are blind and have non-24 hour sleep-wake disorder (low quality evidence).
- Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder (moderate quality evidence).
- There was insufficient evidence to inform recommendations for other treatments or other subpopulations of people with intrinsic circadian rhythm sleep-wake disorders.

Recommendations:

- Due to limited evidence of benefit for circadian rhythm sleep-wake disorders, continue to limit prescription drug use to FDA-labeled and funded indications.
- If drug treatment is medically necessary for funded circadian rhythm sleep-wake disorders or circadian rhythm sleep-wake disorders covered under EPSDT, consider coverage of a melatonin agonist or melatonin before trial of stimulants or other sedating drugs (**Appendix 4**).
- Make at least one melatonin agonist preferred. After evaluation of melatonin agonists in executive session, designate ramelteon tablets as preferred.

Previous Reviews and Current Policy

- In 2020, a systematic review evaluated evidence for sleep disturbances in patients with dementia.[9] Irregular sleep-wake rhythm disorder is common in patients with neurodegenerative and neurodevelopmental disorders, though this study did not specify the specific types of sleep disorders diagnosed in this review. They identified low quality evidence that trazodone 50 mg may improve sleep efficiency and total sleep time (mean difference [MD] 42.46 minutes, 95% CI 0.9 to 84.0) with short-term treatment (2 weeks).[9] Trazodone was not included in this updated literature search for Orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (based on moderate quality evidence).[9] Other sleep outcomes demonstrated no difference from placebo. Ramelteon and melatonin did not demonstrate any change in sleep outcomes based on low quality evidence.[9] No studies evaluated other commonly prescribed therapies such as benzodiazepines or benzodiazepine receptor agonists (e.g., eszopiclone, zolpidem, zaleplon).
- A systematic review evaluating use of melatonin for sleep disorders in adults who are blind found insufficient evidence for efficacy and safety of melatonin.[7]
- Tasimelteon oral suspension was FDA approved in December 2020 for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age based on results from one small, crossover, placebo-controlled trial (n=25) evaluating treatment over 4 weeks.[10] Smith-Magenis Syndrome is a funded condition on the prioritized list. The primary outcomes were subjective total sleep time and nighttime sleep quality (reported by the patient's parent/guardian) for the 50% of nights with the worst sleep.[10] Sleep quality was rated on a 5 point scale from excellent (5) to poor (1). Compared to placebo, tasimelteon treatment resulted in improved sleep quality for the 50% of nights with the worst sleep quality though magnitude of benefit was small (2.8 vs. 2.4; least square mean difference 0.4 [95% CI 0.1 to 0.7]).[10] The difference from placebo in total sleep time for the 50% of nights with the worst sleep was not statistically improved with tasimelteon (7 vs. 6.7 hours; least square mean difference 0.3 [95% CI -0.0 to 0.6]).[10]
- In Fee for Service (FFS), all sedative drugs require prior authorization (PA). For treatment of chronic insomnia, the Health Evidence Review Commission (HERC) has recommended coverage of sedative hypnotics not exceeding 30 days every year. Melatonin is currently covered for people up to 18 years of age without PA. Melatonin is not covered for adults because it has not demonstrated improvement in symptoms compared to placebo for treatment of insomnia.
- Armodafinil and modafinil are carved-out of coordinated care organizations (CCOs) and require PA which limits use to funded conditions with documented evidence of benefit. Caffeine tablets (available over the counter) can be covered by FFS when prescribed by a provider.

Background:

Circadian rhythm sleep-wake disorders are defined as sleep disruption caused by misalignment of a person's internal circadian rhythm and the external environment.[2] The internal (or intrinsic) circadian sleep rhythm is typically slightly longer than 24 hours for most people and is synchronized (or entrained) to a 24 hour period by the 24-hour dark-light cycle and secretion of melatonin, a pineal hormone.[2] Food and exercise have a more modest effect on the circadian rhythm. Failure to synchronize to this 24-hour period can lead to circadian rhythm sleep-wake disorders.[2]

Circadian rhythm sleep-wake disorders are classified based whether on the primary driver of the disorder is internal (intrinsic) or external (environmentally-influenced).[2] For example, shift work disorder and jet lag are common circadian rhythm sleep-wake disorders that are classified as extrinsic disorders. Common intrinsic disorders include advanced sleep phase disorder, delayed sleep phase disorder, irregular sleep-wake rhythm disorder, or non-24 hour sleep-wake syndrome. These are most commonly diagnosed based on clinical history, sleep logs and actigraphy. The diagnostic criteria for circadian rhythm sleep-wake disorders includes recurrent symptoms of insomnia, sleepiness or both caused by misalignment of the endogenous circadian rhythm and the individual's external environment or schedule. Polysomnography may be used to rule out other related sleep conditions, but is not usually recommended to diagnose circadian rhythm sleep-wake disorders.

Extrinsic circadian rhythm sleep-wake disorders are defined based on their external cause. Jet lag disorder is categorized as a temporary disorder related to travel across time zones creating misalignment between the desired sleep time in the new time zone and the endogenous circadian sleep-wake cycle. Symptoms typically worsen when traveling in an eastward direction and across multiple time zones. Shift work disorder occurs when a person's work schedule overlaps with usual sleep time. It is estimated that about 15% of salaried workers in the United States work on shifts including nights.[1] Shift work is generally common in younger people and prevalence varies based on the job. Some of the most common jobs that rely on shift work include healthcare and transportation industries. In people with shift work disorder, symptoms are usually present for at least 1 month and associated with functional impairment or significant distress. It is estimated that people working night shifts are more likely to fall asleep at work or experience insomnia symptoms compared to people working during the day (10% vs. 7%).[1]

Intrinsic circadian rhythm sleep-wake disorders are typically defined based on the timing of sleep and wake symptoms. Delayed sleep-wake phase disorder is characterized by a delay in the major sleep episode compared to the desired sleep schedule.[2] This results in excessive sleepiness when waking at the desired time and insomnia symptoms when trying to sleep at the desired time, but quality of sleep is typically reported as normal if sleeping on the delayed schedule. Advanced sleep-wake disorder is characterized by the opposite sleep pattern with excessive sleepiness in the evening before the individual's usual bedtime and insomnia symptoms in the early morning before the individual would normally be awake.[2] Non-24 hour sleep-wake disorder is diagnosed when an individual fails to entrain to a 24-hour cycle resulting in a gradually shifting sleep-wake pattern over time. As the internal circadian rhythm shifts, individuals experience hypersomnolence during the day and insomnia symptoms at night.[2] This is most common in individuals who are totally blind and lack external input from the 24-hour light-dark cycle. However, non-24 hour sleep-wake disorder has been documented in individuals who are sighted.[2] Irregular sleep-wake rhythm disorder does not have a clearly defined sleep-wake pattern. Symptoms typically include prolonged periods of wakefulness during the night and excessive sleepiness during the day with fragmented sleep. Irregular sleep-wake rhythm disorder is most commonly diagnosed in people with neurodevelopmental or neurodegenerative disorders.[2] For all intrinsic disorders, diagnosis typically requires documentation of sleep and insomnia symptoms for at least 7-14 days by actigraphy or sleep diary.[2]

The goal of treatment for circadian rhythm sleep-wake disorders is to realign the endogenous sleep-wake cycle with the desired external schedule to improve daytime functioning. Common outcomes evaluated in clinical trials include changes in biologic markers of circadian rhythm, total sleep time, sleep latency (or

the time it takes to fall asleep), sleep quality, and sleep onset and offset times. There are no well-established standards for minimum clinically important differences in these outcomes for people with circadian rhythm sleep-wake disorders.[2] In 2015, the American Academy of Sleep Medicine defined significance thresholds based on expert consensus that were critical for evaluating and making recommendations for intrinsic circadian rhythm sleep-wake disorders (**Table 1**).[2]

Table 1. AASM-defined clinical significance thresholds for outcomes that were critical for guideline recommendations[2]

Disorder	Change in circadian phase or total sleep time	Change in sleep onset, offset or sleep latency	Entrainment status
Advanced sleep-wake disorder Delayed sleep-wake disorder Irregular sleep rhythm disorder	30 minutes	15 minutes	N/A
Non-24 hour sleep-wake disorder	N/A	N/A	Yes/No

Abbreviation: AASM = American Academy of Sleep Medicine; N/A = not applicable

For some people total sleep time may be unchanged, but patients experience excessive sleepiness when they want to be awake, and experience insomnia symptoms when they want to sleep. In these circumstances, sleep latency and sleep onset/offset times may be a better marker of symptoms than total sleep times. Sleep quality, wakefulness, and excessive sleepiness can also be evaluated using a wide variety of tools and scales. One of the more common scales used to evaluate excessive sleepiness in circadian rhythm disorders is the Karolinska Sleepiness Scale (KSS). The KSS ranges from 1 (extremely alert) to 5 (neither alert nor sleepy) to 9 (very sleepy, great effort keeping awake).[11] There is no well-established minimum clinically important difference referenced in literature for KSS. In many clinical trials, the circadian rhythm can be evaluated using excretion of urinary or salivary melatonin concentrations (referred to as the dim light melatonin onset or the start of endogenous melatonin production during dim light conditions). However, it is not clear whether endogenous secretion of melatonin correlates well with symptoms of insomnia or function in all conditions. Several studies have evaluated dim light melatonin onset but results do not consistently correlate with improvement in symptoms of insomnia, alertness, sleep quality, or daytime function.[12] Historically, the FDA has not accepted biomarkers of urinary melatonin excretion as relevant outcomes for FDA approval of drug treatment for circadian rhythm sleep-wake disorders.[10]

Treatments for circadian rhythm sleep-wake disorders fall broadly into 4 categories including:[2]

- Prescribed timing of the sleep-wake schedule or timed physical activity/exercise
- Strategic avoidance or receipt of light
- Use of medications or supplements to shift the sleep-wake cycle or promote alertness
- Somatic interventions to alter bodily functions and impact sleep-wake behaviors

Timed administration of bright light can help to prevent symptoms of excessive sleepiness. A variety of factors can influence efficacy of light exposure including timing and duration of exposure, prior light exposure or "light history", and light intensity and light wavelength.[2] Sedating drugs (most commonly melatonin) have also been used prior to the desired sleep time to prevent insomnia symptoms. The optimal dose of melatonin has not been determined, and some studies suggest that the timing of melatonin administration may be more important than the dose.[2] In some types of circadian rhythm sleep-wake disorders, stimulants such as modafinil, armodafinil or caffeine have also been used to improve alertness after waking. Drugs that are FDA-approved for circadian rhythm sleep-wake disorders include stimulants (e.g., modafinil, armodafinil) indicated to improve wakefulness in for shift work disorder and tasimelteon indicated for non-24 hour sleep-wake disorder. **Table 2** describes studies evaluated for FDA approval of these drugs**.** Other stimulants and sedating drugs are indicated for related

conditions to improve excessive sleepiness associated with narcolepsy or decrease symptoms of insomnia, but are not specifically FDA-approved for circadian rhythm sleep-wake disorders. Randomized controlled trials (RCTs) have also been completed which evaluate use of stimulants or melatonin receptor agonists in patients with jet lag disorder and irregular sleep-wake rhythm disorder,[12-15] but these agents have not yet been FDA approved for these conditions. In Europe, regulatory approval of modafinil and armodafinil for shift work disorder was withdrawn in 2010 as a result of serious adverse events including neuropsychiatric disorders and fatal skin reactions associated with treatment.[1] European regulatory agencies concluded that benefits of modafinil and armodafinil only outweigh risks when used in patients with narcolepsy.

Historically, insomnia and circadian rhythm sleep-wake disorders have been unfunded on the HERC prioritized list of health services. In 2022, HERC recommended changes to expand non-pharmacological coverage for insomnia and limit duration of drug coverage for insomnia. These changes limit drug coverage of sedative hypnotics to 30 days for treatment of insomnia. In FFS Medicaid, melatonin is covered for people up to 18 years of age, but is not covered for adults due to lack of documented benefit for common sleep disorders like insomnia. Prior authorization is required for all sedatives and stimulants with indications for sleep disorders (e.g., modafinil and armodafinil). These drugs can be covered for unfunded sleep conditions if the sleep disorder is related to a comorbid funded condition and standard treatments for the funded condition were inadequate to control symptoms.

Table 2. Summary of Studies Evaluated for FDA-Approval of Common Circadian Rhythm Sleep-Wake Disorders

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th><th>Notes/Limitations</th></tr>
<tr>
<td>Lockey, et al. 2015.[16]

MC, DB, PC, RCT

Duration:
SET: 26 weeks
RESET: 11 weeks</td>
<td>SET:
1. Tasimelteon 20 mg 1 hour before bedtime (n=42)
2. Placebo (n=42)

RESET: Withdrawal Study
1. Continue tasimelteon 20 mg (n=10)
2. Withdraw to placebo (n=10)</td>
<td>Adults who were blind with non-24H sleep-wake disorder

27 sites in the US and 6 sites in Germany</td>
<td><u>Primary Outcome</u>
Proportion of patients entrained (SET) or who maintain entrainment (RESET)

<u>Relevant Secondary Outcomes Evaluated for FDA approval</u>[10]
Change in total sleep time during the day or night on most symptomatic days/nights</td>
<td>Entrainment
<table>
<tr><th></th><th>SET</th><th>RESET</th></tr>
<tr><td>1.</td><td>8/40 (20%)</td><td>9/10 (90%)</td></tr>
<tr><td>2.</td><td>1/38 (3%)</td><td>2/10 (20%)</td></tr>
<tr><td></td><td>Difference 17% 95% CI 3.2-31.6; p=0.0171</td><td>Difference 70% 95% CI 26.4-100; p=0.0026</td></tr>
</table>
Change from baseline in sleep time on 25% most symptomatic days/nights (minutes)
<table>
<tr><th>SET</th><th>Nighttime</th><th>Daytime</th></tr>
<tr><td>1.</td><td>50</td><td>-49</td></tr>
<tr><td>2.</td><td>22</td><td>-22</td></tr>
</table>
<table>
<tr><th>RESET</th><th>Nighttime</th><th>Daytime</th></tr>
<tr><td>1.</td><td>-7</td><td>-9</td></tr>
<tr><td>2.</td><td>-74</td><td>50</td></tr>
</table>
</td>
<td>Randomized via interactive voice response system. Baseline characteristics balanced. Blinded with matching placebo. High attrition 24% and 28% in treatment and placebo groups, respectively. Outcomes reported as specified, but a secondary, post-hoc outcome was used for FDA approval. Industry funded.

Ethnicities other than white (81-86%) were underrepresented. Patients with any significant medical or psychiatric disorders were excluded. Of 391 patients evaluated, 136 (35%) were enrolled in the screening period and 84 (62% of enrolled) were randomized.</td>
</tr>
</table>

Czeisler 2005. [5] MC, DB, PC, RCT N=209 Duration: 3 months	1. Modafinil 200 mg taken 30-60 minutes before the night shift (n=110) 2. Placebo (n=99)	Adults with SWD and moderate to severe excessive sleepiness during the night shift for at least 3 months, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%) 39 centers in the US between December 2001 and September 2002	<u>Primary</u> CGI-C (range 1-7) MSLT <u>Secondary</u> Psychomotor vigilance test KSS (range 1-9)	CGI-C at least minimally improved 1. 74% 2. 36% P<0.001 Change in MSLT from baseline 1. 1.7±0.4 minutes; P<0.001 2. 0.3±0.3 minutes; P=0.24 Psychomotor vigilance test (change from baseline in number of lapses of attention in 20 minutes) 1. -2.6 lapses 2. 3.8 lapses P=0.005 for difference at final visit Change in KSS from baseline 1. -1.5±0.2 2. -0.4±0.2 P<0.001 Patients with accidents or near accidents (reported in patient diary) 1. 46 (29%) 2. 58 (54%) Severe adverse events 1. 6 (5%) 2. 5 (5%)	Randomization method unspecified. Baseline characteristics balanced. Blinded with matching placebo. Per protocol analysis used with attrition of 25% over 3 months. Industry funded. Of 609 patients screened, 209 (34%) were randomized. Most common reasons for exclusion were failure to meet disease severity markers for polysomnography or sleep latency (n=160, 40%). Average sleep latency was about 2 minutes at baseline. Despite some improvement with modafinil, sleep latency remained below 6 minutes, which indicates excessive sleepiness even with treatment.
Czeisler, et al. 2009.[4] MC, DB, PC, RCT N=254 Duration: 12 weeks	1. Armodafinil 150 mg taken 30-60 minutes before the night shift (n=123) 2. Placebo (n=122)	Night shift workers with moderate-severe SWD, ≥3 months of excessive sleepiness during their shift, mean sleep latency ≤6 minutes, and insomnia symptoms during the day (sleep efficiency ≤ 87.5%)	<u>Primary</u> CGI-C (range 1-7) MSLT	CGI-C at least minimally improved 1. 89 (79%) 2. 61 (59%) P=0.001 Change in MSLT from baseline 1. 3.1 minutes (SD 4.5) 2. 0.4 minutes (SD 2.9) Severe Adverse Events 1. 12 (10%) 2. 3 (2%)	Randomization method unspecified. Baseline characteristics balanced Blinded with matching placebo. Assessment of MSLT blinded. Attrition of 31% in placebo and 24% in armodafinil group. Per protocol analysis included only patients with baseline and at least one outcome assessment. Industry funded. Patients were excluded if there was a history of substance abuse, psychiatric disorders, caffeine consumption more than 600mg/day (~6 cups). Of 747

		42 centers in US and Canada from April to December 2004			patients screened, 254 (34%) were randomized. Severe adverse events were determined by site investigator and included diarrhea, low back pain, and suicidal ideation.

Abbreviations: CGI-C = clinical global impression of change; CI = confidence interval; DB = double blind; FDA = Food and Drug Administration; H = hour; KSS = Karolinska Sleepiness Scale, MC = multi-center; MSLT = mean sleep latency test; PC = placebo-controlled; RCT =randomized controlled trial; SWD = shift work disorder; US = United States

Methods:

A Medline literature search for new systematic reviews and 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 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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.

Systematic Reviews:

Non-24 Hour Disorder

An evidence review was developed by NICE 2021 evaluating use of melatonin for treatment of sleep disorders in adults who are blind.[7] Three studies were identified and included in the review (one RCT and 2 crossover studies).[7] The single RCT did not have adequately reported randomization methods which may increase risk of bias.[7] All studies were small (with the largest enrolling 13 participants) and were likely underpowered to determine differences between groups.[7] All identified studies were of short duration (maximum 12 weeks) with long-term efficacy and safety unknown.[7] Overall, 2 studies (n=20) found no significant improvement in total sleep time with 2 mg or 10 mg of melatonin. One study reported a statistically significant improvement in total sleep time of 0.65 hours (about 40 minutes) with use of melatonin 0.5 mg compared to placebo.[7] Two studies reported melatonin decreased the time spent awake after sleep onset by 0.56 hours with melatonin 0.5 mg and 1.3 hours with melatonin 10 mg.[7] No studies identified a difference with melatonin compared to placebo for sleep latency or quality of life. Overall, authors concluded that evidence is insufficient to determine efficacy and safety for use of melatonin in adults who are blind.[7]

A 2011 Cochrane review evaluated efficacy and safety of melatonin for treatment of sleep disorders in children who are visually impaired.[8] Searches were conducted through July 2011 and failed to identify any RCTs evaluating use of melatonin in this population.[8] Identified literature included non-randomized case series studies, studies in adults who were blind, or studies that included mixed populations where results for the visually impaired cohort could not be independently evaluated.[8] Authors concluded that there was insufficient evidence to support or refute the use of melatonin for sleep disorders in visually impaired children.[8]

Shift Work Disorder - Cochrane

A 2014 Cochrane review evaluated pharmacological interventions for symptoms caused by shift work disorder.[1] Fifteen RCTs were included in the review, and pharmacologic interventions included melatonin (n=9), sedative hypnotics (n=2), modafinil (n=1), armodafinil (n=2), and caffeine combined with pre-shift naps (n=1).[1] Data from these trials was limited by lack of methodological reporting on blinding methods and allocation concealment. Five RCTs had high discontinuation rates (>30%), and there was high risk for selective outcome reporting in multiple trials.[1] When multiple measures were used to evaluate sleepiness or alertness, results for a specific measure were rarely reported when the outcome did not differ from placebo.[1] All included trials were limited by short durations (<7 days) and the long-term efficacy and safety of these treatments for shift work disorder is unclear.

In 7 of the 9 RCTs evaluating melatonin, participants had no reported sleeping problems at enrollment which limits applicability of these results.[1] Doses of melatonin ranged between 1 and 10 mg, and were typically administered after the work shift before going to sleep. Eight trials utilized a cross-over study design, and all RCTs evaluated efficacy of melatonin after one or several consecutive night shifts.[1] Outcomes of total sleep time and sleep onset latency were most commonly reported via patient diaries. There was low quality evidence that melatonin may increase self-reported total sleep time by an average of 24 minutes (95% CI 9.8 to 38.9; 7 RCTs; n=263) during the day after administration and 17 minutes (95% CI 3.71 to 30.22; 3 RCTs; n=234) the night after administration, but did not improve sleep latency or sleep quality compared to placebo.[1] Only one RCT evaluated objective sleep time via actigraphy with no difference in duration of sleep.[1]

RCTs of modafinil and armodafinil enrolled shift workers with SWD and moderate to severe excessive sleepiness (mean sleepiness score of 6 to 6.7 points in the placebo group on the 1 to 9 point KSS scale).[1] Most participants (87-93%) had permanent shift work (vs. rotating shifts). The effect of armodafinil (up to 150 mg) and modafinil (200mg) was evaluated over 3-4 days for outcomes of sleepiness (evaluated via KSS or mean sleep latency test [MSLT]) and alertness (evaluated by reaction time).[1] There was moderate quality evidence that armodafinil and modafinil decreased sleepiness during the night shift evaluating using the KSS scale (MD -0.89, 95% CI -1.37 to -0.4 for armodafinil; MD -0.90, 95% CI -1.45 to -0.35 for modafinil).[1] Serious adverse events were more common with armodafinil than placebo (9.7% vs 2.4%; RR 3.97; 95% CI 1.15 to 13.71). Common adverse events included headache and nausea for both stimulants and insomnia for modafinil. In a long-term extension study of armodafinil, about 11% of patients discontinued treatment due to adverse events.[1] Cardiovascular adverse events and clinically relevant increases in blood pressure were also observed in 6% and 18% of patients prescribed armodafinil, respectively.[1] Serious skin reactions, some of which were fatal, and development of psychiatric disorders including suicidal ideation were also documented in post-marketing studies of modafinil[17] and armodafinil[18] resulting in withdrawal of licensing for the indication of shift work disorder in Europe.[1]

Two small studies (n=88) evaluated the impact of hypnotics (zopiclone and lorazepam) on duration of sleep after a work shift in people with sleeping problems.[1] Outcomes were evaluated after 3 or 7 consecutive days for zopiclone and lorazepam, respectively.[1] There was low quality evidence that zopiclone does not improve total sleep time compared to placebo.[1] Patients prescribed lorazepam may be more likely to have a normal sleep pattern than placebo (89% vs. 64%), but statistical differences were not reported between groups.[1]

A 2010 Cochrane review evaluated caffeine for the prevention of injuries and errors caused by impaired alertness in people with jet lag or shift work disorder.[6] The most common dose administered was 200-400 mg, but doses varied across trials and some trials included weight based dosing.[6] Thirteen RCTs were included, though injuries were not reported as an outcome. Only 2 trials evaluated errors and others assessed cognitive performance using a variety of tests. Data were limited by unclear methods for randomization (6 RCTs), allocation concealment (9 RCTs), inadequate information to assess missing data (11 RCTs), and selective outcome reporting (5 RCTs).[6] Most trials were conducted under simulated conditions limiting applicability to real world settings. Compared to placebo, caffeine improved memory (SMD -1.08; 95% CI -2.07 to -0.09, P = 0.03) and orientation and attention (SMD -0.55; 95% CI -0.83 to -0.27, P0.0001), but did not

demonstrate improvement in concept formation and reasoning, verbal functioning and language skills, or perception.[6] Two trials assessed errors with night-time driving and flight simulation with less errors made if people were administered caffeine compared to placebo. Only one RCT was identified comparing caffeine to each of the following other interventions: naps, bright light, and modafinil.[6] These limited studies did not identify any differences in cognitive performance between treatments.[6] Adverse effects associated with caffeine which were more common than placebo included disruption of subsequent sleep and risk for dependence. Authors conclude that caffeine may improve performance but the degree to which this might reduce injury risk is unknown.[6]

Jet Lag

A 2020 systematic review evaluated pharmacologic and non-pharmacologic treatments for travel fatigue and jet lag in athletes.[3] If the initial literature search failed to identify targeted studies in athletes, then the scope of the search was expanded to healthy populations and evidence was downgraded for applicability. Fourteen RCTs and 8 observational studies evaluated management of jet lag and were included in the review.[3] Eleven studies focused on pharmacological interventions conducted under simulated (n=3) or actual (n=9) travel conditions.[3] Pharmacologic treatments included melatonin (n=2), sedatives (n=1), stimulants (n=4), and melatonin agonists (n=4).[3] There were no studies identified which evaluated travel fatigue. Because of heterogeneous study design, populations, flight direction, outcomes measured and statistical parameters, results were summarized descriptively and a meta-analysis was not conducted. The majority of studies enrolled healthy populations, and only a few studies (n=3) evaluated pharmacologic treatments specifically in athletes.[3] RCTs and observational studies of non-pharmacological interventions had high risk of bias and concerns identified with directness, consistency, precision and publication bias. Most RCTs of pharmacologic interventions were evaluated as having low to moderate risk of bias, and methodologic quality of all observational studies was poor. Major evidence limitations included concerns for consistency, precision, and publication bias.[3]

- There was insufficient evidence for use of melatonin in jet lag symptoms in athletes. Evidence was based on 2 single-arm studies with small sample sizes and no comparator group that had mixed results for management of jet lag.[3]
- There was insufficient evidence for use of sedatives in management of jet lag in athletes. A single observational study was identified that evaluated temazepam for travel symptoms.[3]
- No studies evaluated stimulants or melatonin analogues in athletes. In healthy populations, there was moderate quality evidence from 4 RCTs that stimulants (e.g., armodafinil or caffeine) increased alertness and improve resynchronization of the circadian rhythm.[3]
- There were mixed results for use of melatonin agonists to improve jet lag symptoms following travel in healthy populations. Results from 2 RCTs in tasimelteon showed improved sleep symptoms compared to placebo.[3] There were mixed results in 2 studies of ramelteon for jet lag symptoms. In one study of ramelteon, sleep onset was improved with low doses (1 mg) but not high doses (4-8 mg), alertness was improved with 4mg dose but not low (1 mg) or high (8 mg) doses, and all doses decreased scores on the immediate memory recall test.[3] In the second RCT, there was an observed phase shift in the circadian rhythm with 1-4 mg ramelteon compared to placebo, but no difference in jet lag symptoms.[3]

Authors generally concluded that available evidence for management of jet lag in athletes was of low quality and additional studies were required to draw valid conclusions.

After review, 12 systematic reviews were excluded due to poor methodologic quality (e.g., network meta-analyses),[19-30] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

Practice guidelines from the American Academy of Sleep Medicine for the treatment of intrinsic circadian rhythm sleep-wake disorders were updated in 2015.[2] Recommendations were graded as strong or weak recommendations based on degree of clinical certainty regarding net health benefits or harms. For many interventions, there was insufficient evidence to support a recommendation for therapy. There was evidence to support interventions in these populations:

- In adults with advanced sleep-wake phase disorder, evening light therapy is weakly recommended (very low quality evidence).[2]
- In adults, adolescents, and children with delayed sleep-wake phase disorder, strategically timed melatonin or melatonin agonists are weakly recommended (low quality evidence for adults; low-moderate quality evidence for children and adolescents). In children or adolescents, post-awakening light therapy is also weakly recommended (low quality evidence).[2]
- In adults who are blind and have non-24 hour sleep-wake disorder, there is a weak recommendation for strategically timed melatonin or melatonin agonists (low quality evidence).[2]
- In elderly adults with irregular sleep-wake rhythm disorder and dementia, light therapy is weakly recommended (very low quality evidence). There are recommendations against the use of sleep-promoting medications (strong recommendation), melatonin or melatonin agonists (weak recommendation), and combined light therapy and melatonin (weak recommendation) in this population (low to very low quality evidence).[2]
- In children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder, melatonin or melatonin agonists are weakly recommended (moderate quality evidence).[2]

Additional Guidelines for Clinical Context:
Recommendations for extrinsic circadian rhythm sleep-wake disorders were included in practice parameters published by the American Academy of Sleep Medicine in 2007.[31] Because recommendations for intrinsic sleep-wake disorders were updated in 2015,[2] this summary focuses on recommendations for extrinsic disorders (e.g., shift work disorder and jet lag). Recommendations were based on a systematic review of the literature and graded based on evidence. Recommendations were categorized based on certainty of evidence (**Table 3**).[31] This summary will focus on "standard" or "guideline" recommendations.

Table 3. Evidence grades and levels of evidence for Guideline Recommendations[31]

Strength of Recommendation	Degree of Clinical Certainty	Supporting Level of Evidence
Standard	High	High quality RCTs on well-characterized patients or overwhelming evidence from multiple flawed RCTs and/or cohort studies
Guideline	Moderate	Evidence from a cohort study or flawed clinical trial, or consensus from multiple case control studies
Option	Uncertain	Inconclusive or conflicting evidence or conflicting expert opinion. Clinical benefits or risks in this population are uncertain.

Two treatment recommendations were supported by standard recommendations with high quality evidence from well-designed RCTs:

- Planned sleep schedules are recommended in people with shift work disorder.[31] Several lab simulation and observational studies have demonstrated that napping prior to a work night shift will improve alertness, reaction time, and work accidents without affecting post-shift daytime sleep.
- Timed melatonin administration is recommended for people with jet lag disorder.[31] In several studies, melatonin has demonstrated improvements in duration of sleep and sleep quality compared to placebo, with mixed results for improvement of jet lag symptoms. The most effective dose of melatonin is unclear and one study demonstrated decreased efficacy after more than 3 days of use post-travel.

Several treatment recommendations were supported by guideline recommendations with moderate quality evidence from flawed RCTs or observational studies

- Timed light exposure is recommended in people with shift work disorder.[31] In shift work disorder, several studies utilizing a variety of light intensities and durations have demonstrated that administration of bright light for during the work shift demonstrate improvements in timed work performance tasks, alertness, and mood compared to ordinary light exposure. There is mixed evidence for improvements in daytime sleep in patients with shift work disorder.
- Timed melatonin is recommended in people with shift work disorder.[31] In shift work disorder, several studies have shown that melatonin administered prior to sleep after a work shift improved daytime sleep quality and duration, but failed to improve alertness during the work shift.
- Hypnotics (for insomnia symptoms) or alerting agents like modafinil are recommended in people with shift work disorder.[31] Hypnotics evaluated for shift work disorder included triazolam, temazepam, and zolpicone and generally demonstrated improvements in duration of sleep and sleep quality with inconsistent effects on alertness during the work shift. Authors caution that risks of hypnotics should be weighed against benefits as hypnotics could worsen comorbid conditions. Stimulants like modafinil have shown improved psychomotor performance and alertness during night shifts, but are not a substitute for adequate sleep and have the potential to impair daytime sleep periods.

Randomized Controlled Trials:

A total of 127 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), outcome studied (eg, non-clinical), or inclusion in systematic reviews and guidelines.

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Appendix 1: Preferred Drug List

Sedatives

Generic	Brand	Form	PDL
melatonin	MELATONIN	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
daridorexant HCl	QUVIVIQ	TABLET	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N

triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N
chloral hydrate	CHLORAL HYDRATE	SYRUP	
dexmedetomidine HCl	IGALMI	FILM	
melatonin/pyridoxine HCl (B6)	MELATONIN-VITAMIN B6	TABLET	

Other Stimulants

Generic	Brand	Form	PDL	Carveout
armodafinil	ARMODAFINIL	TABLET	Y	Y
armodafinil	NUVIGIL	TABLET	Y	Y
modafinil	MODAFINIL	TABLET	Y	Y
modafinil	PROVIGIL	TABLET	Y	Y
solriamfetol HCl	SUNOSI	TABLET	V	Y
pitolisant HCl	WAKIX	TABLET	N	

ADHD Drugs

Generic	Brand	Form	PDL	Carveout
atomoxetine HCl	ATOMOXETINE HCL	CAPSULE	Y	Y
atomoxetine HCl	STRATTERA	CAPSULE	Y	Y
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL ER	CPBP 50-50	Y	
dexmethylphenidate HCl	FOCALIN XR	CPBP 50-50	Y	
dexmethylphenidate HCl	DEXMETHYLPHENIDATE HCL	TABLET	Y	
dexmethylphenidate HCl	FOCALIN	TABLET	Y	
dextroamphetamine/amphetamine	ADDERALL XR	CAP ER 24H	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHET ER	CAP ER 24H	Y	
dextroamphetamine/amphetamine	ADDERALL	TABLET	Y	
dextroamphetamine/amphetamine	DEXTROAMPHETAMINE-AMPHETAMINE	TABLET	Y	
lisdexamfetamine dimesylate	VYVANSE	CAPSULE	Y	
lisdexamfetamine dimesylate	VYVANSE	TAB CHEW	Y	
methylphenidate	DAYTRANA	PATCH TD24	Y	
methylphenidate	METHYLPHENIDATE	PATCH TD24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL CD	CPBP 30-70	Y	
methylphenidate HCl	METHYLPHENIDATE HCL ER (CD)	CPBP 30-70	Y	
methylphenidate HCl	CONCERTA	TAB ER 24	Y	

methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	Y	
methylphenidate HCl	METHYLPHENIDATE HCL	TABLET	Y	
methylphenidate HCl	RITALIN	TABLET	Y	
clonidine HCl	CLONIDINE HCL ER	TAB ER 12H	V	Y
guanfacine HCl	GUANFACINE HCL ER	TAB ER 24H	V	Y
guanfacine HCl	INTUNIV	TAB ER 24H	V	Y
viloxazine HCl	QELBREE	CAP ER 24H	V	Y
amphetamine	DYANAVEL XR	SUS BP 24H	N	
amphetamine	DYANAVEL XR	TAB BP 24H	N	
amphetamine	ADZENYS XR-ODT	TAB RAP BP	N	
amphetamine sulfate	EVEKEO ODT	TAB RAPDIS	N	
amphetamine sulfate	AMPHETAMINE SULFATE	TABLET	N	
amphetamine sulfate	EVEKEO	TABLET	N	
dextroamphetamine	XELSTRYM	PATCH TD24	N	
dextroamphetamine sulfate	DEXEDRINE	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE ER	CAPSULE ER	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	SOLUTION	N	
dextroamphetamine sulfate	PROCENTRA	SOLUTION	N	
dextroamphetamine sulfate	DEXTROAMPHETAMINE SULFATE	TABLET	N	
dextroamphetamine sulfate	ZENZEDI	TABLET	N	
dextroamphetamine/amphetamine	MYDAYIS	CPTP 24HR	N	
methamphetamine HCl	DESOXYN	TABLET	N	
methamphetamine HCl	METHAMPHETAMINE HCL	TABLET	N	
methylphenidate	COTEMPLA XR-ODT	TAB RAP BP	N	
methylphenidate HCl	ADHANSIA XR	CPBP 20-80	N	
methylphenidate HCl	METHYLPHENIDATE ER (LA)	CPBP 50-50	N	
methylphenidate HCl	METHYLPHENIDATE LA	CPBP 50-50	N	
methylphenidate HCl	RITALIN LA	CPBP 50-50	N	
methylphenidate HCl	JORNAY PM	CPDR ER SP	N	
methylphenidate HCl	APTENSIO XR	CSBP 40-60	N	
methylphenidate HCl	METHYLPHENIDATE ER	CSBP 40-60	N	
methylphenidate HCl	METHYLIN	SOLUTION	N	
methylphenidate HCl	METHYLPHENIDATE HCL	SOLUTION	N	
methylphenidate HCl	QUILLIVANT XR	SU ER RC24	N	
methylphenidate HCl	QUILLICHEW ER	TAB CBP24H	N	
methylphenidate HCl	METHYLPHENIDATE HCL	TAB CHEW	N	
methylphenidate HCl	METHYLPHENIDATE ER	TAB ER 24	N	
methylphenidate HCl	RELEXXII	TAB ER 24	N	
methylphenidate HCl	METHYLPHENIDATE ER	TABLET ER	N	
serdexmethylphen/dexmethylphen	AZSTARYS	CAPSULE	N	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 03, 2023

1	exp "Hypnotics and Sedatives"/	129148
2	exp Melatonin/	22605
3	exp Doxylamine/	397
4	exp Estazolam/	112
5	ramelteon.mp.	493
6	suvorexant.mp.	347
7	exp Triazolam/	1241
8	zaleplon.mp.	437
9	exp Diphenhydramine/	4516
10	exp Doxepin/	847
11	exp Eszopiclone/	134
12	exp Flurazepam/	781
13	exp Midazolam/	9610
14	exp Zolpidem/	1735
15	exp Dexmedetomidine/	5093
16	daridorexant.mp.	47
17	exp Benzodiazepines/	68872
18	exp central nervous system stimulants/ or exp amphetamine/ or exp dexmethylphenidate hydrochloride/ or exp dextroamphetamine/ or exp methylphenidate/ or exp modafinil/	101793

19	exp Atomoxetine Hydrochloride/	1337
20	exp Clonidine/	13470
21	exp Guanfacine/	751
22	exp Viloxazine/	242
23	serdexmethylphenidate.mp.	5
24	armodafinil.mp.	225
25	solriamfetol.mp.	83
26	pitolisant.mp.	171
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	289392
28	exp Sleep Disorders, Circadian Rhythm/	2685
29	delayed sleep-wake phase disorder.mp.	88
30	advanced sleep-wake phase disorder.mp.	11
31	irregular sleep-wake rhythm disorder.mp.	18
32	non-24 hour sleep-wake rhythm disorder.mp.	18
33	shift work disorder.mp.	153
34	exp Jet Lag Syndrome/	584
35	28 or 29 or 30 or 31 or 32 or 33 or 34	2805
36	27 and 35	632
37	limit 36 to (english language and humans)	537
38	limit 37 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	127

Appendix 3: Key Inclusion Criteria

Population	Circadian Rhythm Sleep Disorders (e.g., delayed or advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, non-24 hour sleep-wake rhythm disorder, shift work disorder, jet lag) in adults and children.
Intervention	Stimulants (**Appendix 1**) Sedatives (**Appendix 1**)
Comparator	Active medication comparators listed in **Appendix 1** or placebo
Outcomes	Symptoms (e.g., excessive daytime sleepiness, amount and quality of sleep) Quality of life Function (e.g., impacts on driving, work, school)
Setting	Outpatient

Appendix 4: Proposed Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions, with individual review for individuals covered under the EPSDT program. Long-term treatment of insomnia with sedatives is not funded.
- Encourage use of cognitive behavioral therapy for insomnia.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) except melatonin in children and adolescents. Melatonin is not covered for adults over 18 years of age.

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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for a non-preferred product and 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. Go to #5	**No:** Go to #5

Approval Criteria		
5. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for 5 years	**No:** Go to #6
6. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch.	**No:** Go to #8
8. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10	**No:** Go to #11

Approval Criteria		
10. Is the patient on CPAP?	**Yes:** Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
11. Is the request for treatment of insomnia?	**Yes:** Go to #12	**No:** Go to #13
12. Is the patient currently engaged in cognitive behavioral therapy focused on insomnia treatment (CBT-I), failed to have benefit in symptoms after 5-6 CBT interventions, OR have inability to access CBT-I?	**First request:** Sedative treatment can be approved for 30 days. Long-term treatment must document that benefits outweigh risks. **Subsequent request:** Go to **Renewal Criteria**	**No:** Pass to RPh. Deny; medical appropriateness.
13. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Yes:** Document supporting literature and approve 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** For current age ≥ 21 years: Deny; not funded by OHP. For current age < 21 years: Go to #14
14. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #15 Document baseline severity	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
15. Is the request for a melatonin agonist (e.g., melatonin, ramelteon, tasimelteon) for treatment of one of the following circadian rhythm sleep-wake disorders: • People with delayed sleep-wake phase disorder • Adults with non-24 hour sleep-wake disorder • Children and adolescents with neurologic disorders and irregular sleep-wake rhythm disorder?	**Yes:** Approve for approve 30 days with subsequent approvals dependent on follow-up and documented response.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a slow taper plan?	**Yes:** Approve for duration of taper (not to exceed 3 months). Subsequent requests should document progress toward discontinuation	**No:** Go to #2
2. Is the request for treatment of an unfunded condition previously approved by FFS?	**Yes:** For current age < 21 years: Go to #3 For current age ≥21 years: Pass to RPh. Deny; not funded by OHP	**No:** Go to #4
3. Is there documentation of improvement (e.g., of symptoms, function, quality of life, etc) since treatment was started?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
4. Is there documentation based on medical records that the patient and provider have discussed whether benefits of ongoing therapy (hospitalizations, function, quality of life) continue to outweigh risks (memory problems, dementia, cognitive impairment, daytime sedation, falls, fractures, dependence, and reduced long-term efficacy)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *12/22 (SS); 8/22; 12/20; 7/18; 3/17; 11/14, 3/14, 5/06, 2/06, 11/05, 9/05, 2/04, 2/02, 9/01*
Implementation: *1/1/23; 10/1/22; 1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Sleep-Wake Medications

Goal(s):
- To promote safe use of drugs for obstructive sleep apnea and narcolepsy.
- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP. Accommodate individual review for individuals under the EPSDT program.
- Limit use to safe doses.

Length of Authorization:
- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit

Requires PA:
- Modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea
- Solriamfetol
- Pitolisant

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/

Table 1. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)
• Excessive daytime sleepiness in narcolepsy	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older	Not FDA approved; insufficient evidence
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil	18 years	250 mg
Modafinil	18 years	200 mg
Solriamfetol	18 years	150 mg
Pitolisant	18 years	17.8 mg (poor CYP2D6 metabolizers)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA-approved for narcolepsy in this age group.
3. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #6	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #5
5. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc) despite lifestyle modifications (e.g., strategic bright light receipt or avoidance, sleep hygiene, dietary changes, etc)?	**Yes:** Document symptom severity. Go to #6 Evidence supports modafinil and armodafinil in moderate-severe shift work disorder (e.g., sleep latency ≤ 6 minutes) and risks likely outweigh benefits in patients with mild symptoms.	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #8
8. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #9	**No:** Go to #10
9. Is the request for pitolisant in a patient with documentation of all the following: • CYP2D6 testing which indicates the patient is not a poor metabolizer • Chart notes or provider attestation indicating lack of hepatic or renal impairment	**Yes:** Go to #10 Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #11 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the request for solriamfetol or pitolisant?	**Yes:** Go to #12	**No:** Go to #16
12. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #13
13. Is the request for solriamfetol?	**Yes:** Go to #14	**No:** Go to #16

Approval Criteria		
14. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #19 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
16. Is the patient of childbearing potential?	**Yes:** Go to #17	**No:** Go to #19
17. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #18
18. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #19	**No:** Pass to RPh. Deny; medical appropriateness.
19. Is the request for treatment of narcolepsy for a drug FDA-approved for the condition (Table 1)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #20
20. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) for a drug FDA-approved for the condition (see Table 1)?	**Yes:** Go to #21	**No:** Go to #22
21. Is the patient compliant with recommended first-line treatments (e.g., CPAP or other primary therapy)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Pass to RPh; Deny; medical appropriateness

Approval Criteria		
22. Is the request for off-label use of armodafinil, solriamfetol, or pitolisant (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #23
23. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #24
23. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for "medical appropriateness". • Evidence to support cognition enhancement is insufficient and should be denied for "medical appropriateness". If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Renewal Criteria		
1. Is the request for solriamfetol?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #4	**No:** Go to #5
4. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit. For Epworth Sleepiness Scale, and improvement of at least 3 points is considered clinically significant.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *4/23; 10/20 (DE); 2/20; 7/19; 03/16; 09/15*
Implementation: *5/1/23; 11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16*