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Drug Class Update: Sleep-wake Medications

Date of Review: October 2025

Date of Last Review: April 2023 (Circadian Rhythm Sleep Disorders)
February 2020 (Other stimulants)
Dates of Literature Search: 1/1/2020 – 5/28/2025

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

Purpose for Class Update:
To evaluate efficacy and safety of medications used to treat central disorders of hypersomnolence and other conditions that cause excessive daytime sleepiness (EDS).

Plain Language Summary:

- Hypersomnolence is an inability to stay awake and alert during normal waking hours leading to uncontrollable drowsiness or unplanned sleep events. People with hypersomnolence have daytime sleepiness that is not simply due to a few nights of lost sleep or after unusual physical action.
- The central nervous system helps control sleep-wake cycles. Some conditions like narcolepsy and hypersomnia disturb the sleep-wake control cycle. They are known as central disorders of hypersomnolence because they prevent the central nervous system's ability to keep a normal balance between sleep and wakefulness.
- Medical conditions such as obstructive sleep apnea may cause difficulty in normal breathing or require assistive breathing devices that upset normal sleep patterns. Other medical conditions such as multiple sclerosis may cause sudden tiredness because of damage to the brain and spinal cord.
- Some medicines called stimulants can help people with daytime sleepiness become more awake and alert. Examples of stimulants used for this purpose include modafinil, armodafinil, solriamfetol, pitolisant, and sodium oxybate.
- These medicines may be prescribed for conditions like narcolepsy, which causes excessive daytime sleepiness and sudden sleep attacks. They can also be used as an add-on therapy for people with other health issues that can cause extreme tiredness. Examples of conditions that use stimulants for add on therapy include cancer, depression, or obstructive sleep apnea.
- Providers must send the Oregon Health Authority (OHA) information to document why they are prescribing modafinil or armodafinil before the Oregon Health Plan (OHP) will pay for the medicine. This process is called prior authorization (PA).

Research Questions:

1. What is the comparative efficacy or effectiveness of medications used to promote wakefulness for patients with narcolepsy, obstructive sleep apnea (OSA), or fatigue due to chronic medical conditions?

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2. What are the comparative harms of treatments for narcolepsy, OSA, or fatigue due to other chronic medical conditions?
3. Are there any subpopulations who would receive more benefit or suffer more harm from drugs for treatment of sleep-wake disorders (e.g., based on disease severity markers, specific types of sleep-wake disorders, or comorbid conditions)?

Conclusions:

- Current PA criteria for modafinil and armodafinil provide coverage for excessive sleepiness related to narcolepsy, obstructive sleep apnea (OSA), cancer, depression, and multiple sclerosis.
- In people with idiopathic hypersomnia, high-quality evidence from one systematic review reported that, compared to placebo, modafinil improved Epworth Sleepiness Scale (ESS) scores (Mean Difference [MD] 5.08 points; 95% confidence interval [CI] 3.01 to 7.16) and resulted in a longer mean sleep latency (MD 4.74 minutes; 95% CI 2.46 to 7.01 minutes longer) at 3 weeks.[1]
- In people with multiple sclerosis (MS), there was moderate-quality evidence that treatment with modafinil led to a reduction in fatigue compared with placebo, as measured by Modified Fatigue Impact Scale (MD = −4.42; 95% CI −8.01 to −.84; p=0.02; 5 studies] and a modest improvement in ESS scores (MD = −0.87; 95% CI −1.64 to −0.10; p=0.03; 3 studies).[2] The clinical significance of a less than one-point change on the ESS is unclear. Post-treatment overall physical quality of life (QoL) score was higher after modafinil treatment compared to placebo (standard mean difference [SMD] = 0.27; 95% CI 0.07 to 0.46; p=0.007; 4 studies).[2] Patients treated with modafinil had a higher risk of an adverse event compared to placebo (relative risk [RR] = 1.30; 95% CI 1.03, 1.66; p=0.03; 4 studies).[2] The most commonly reported adverse events were gastrointestinal disturbances and insomnia.[2]
- Guidelines from the American Academy of Sleep Medicine (AASM) (2021) recommended the following sleep wake agents for treatment of central disorders of hypersomnolence in adults and children.[3] Strong recommendations were based on higher quality evidence and conditional recommendations were based on lower-quality evidence.[3]
    - Modafinil
        - narcolepsy in adults (STRONG) and pediatric patients (CONDITIONAL)
        - idiopathic hypersomnia in adults (STRONG)
        - hypersomnia secondary to Parkinson's disease in adults (CONDITIONAL)
        - hypersomnia secondary to traumatic brain injury in adults (CONDITIONAL)
        - multiple sclerosis in adults (CONDITIONAL)
    - Armodafinil
        - multiple sclerosis in adults (CONDITIONAL)
        - traumatic brain injury in adults (CONDITIONAL)
    - Pitolisant
        - narcolepsy in adults (STRONG)
        - idiopathic hypersomnia in adults (CONDITIONAL)
    - Solriamfetol
        - narcolepsy in adults (STRONG)
    - Sodium oxybate
        - narcolepsy in adults (STRONG)
        - idiopathic hypersomnia in adults (CONDITIONAL)
        - hypersomnia secondary to Parkinson's disease in adults (CONDITIONAL)
        - narcolepsy in pediatric patients (CONDITIONAL)

- Guidelines from the National Institute for Health and Clinical Excellence (NICE) recommended modafinil for management of the following:[4,5]
    - Use for daytime sleepiness due to Parkinson's disease if sleep history has excluded reversible pharmacological and physical causes.[4]
    - Use for fatigue due to multiple sclerosis after consideration of patient needs, priorities, and preferences and assessment of potential risks, benefits, and safety.[5]
    - Should not be used in pregnancy or if planning to become pregnant due to risk of malformations. Effective birth control methods are necessary during treatment and for up to two months after treatment discontinuation.[4,5] Use alternate forms of contraception due to reduced effectiveness of hormonal contraceptives.[4,5]
- Guidelines from the Department of Veterans Affairs and Department of Defense (VA/DoD) found evidence for the following sleep-wake agents for treatment of hypersomnia associated with OSA:[6]
    - Modafinil and armodafinil improve the critical outcomes of sleepiness and quality of life (moderate-quality evidence)
    - Solriamfetol improve sleepiness (moderate-quality evidence) and quality of life (high-quality evidence)
      Recommendation:
        - Suggest the addition of modafinil, armodafinil, or solriamfetol to treat OSA-related residual excessive daytime sleepiness in patients optimally treated with sufficient primary therapies (e.g. mandibular advancement devices, positive airway pressure [PAP], etc.) (Weak recommendation/moderate- to high-quality evidence).[6]

Expanded Indications and New Formulations

- October 2018: XYREM (sodium oxybate) oral solution received expanded approval for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.[7]
- October 2020: WAKIX (pitolisant) received expanded approval for the treatment of EDS or cataplexy in adult patients with narcolepsy.[8]
- August 2021: XYWAV (sodium oxybate) received expanded approval for the treatment of idiopathic hypersomnia (IH) in adults.[9]
- May 2023: LUMRYZ (sodium oxybate) extended-release oral suspension received FDA-approval for the treatment of cataplexy or EDS in adults with narcolepsy.[10]
- June 2024: WAKIX, received expanded approval for treatment of EDS in pediatric patients 6 years of age and older with narcolepsy.[8]
- September 2024: LUMRYZ (sodium oxybate) received expanded approval for the treatment of narcolepsy in patients 7 years and older.[11]

Recommendations:

- Add all sodium oxybate formulations to the Sleep-wake Medication class on the Preferred Drug List (PDL).
- After review of costs in executive session, no changes to PDL were made.
- Review and update PA criteria as proposed and apply criteria to all sodium oxybate formulations.

Summary of Prior Reviews and Current Policy:

- Previous reviews have not identified clinically significant comparative differences in efficacy or harms between agents for narcolepsy including modafinil, armodafinil, pitolisant, solriamfetol, or sodium oxybate. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, incidence of cataplexy attacks, quality of life, adverse reactions) or off-label dosage consideration to delineate any changes to preferred or non-preferred status. Modafinil and armodafinil are stimulants which have been studied for circadian rhythm sleep-wake disorders including shift work disorder. There is insufficient direct evidence to evaluate comparative efficacy or safety of modafinil, armodafinil, or other stimulants for shift work disorder or in the treatment of other circadian rhythm sleep-wake disorders. Currently modafinil, armodafinil, and solriamfetol are carve-out medications and paid for by the Oregon Medicaid fee-

for-service (FFS) program. Modafinil and armodafinil are designated as preferred and solriamfetol as voluntary non-preferred on the OHP preferred drug list (PDL). Sodium oxybate and pitolisant are classified as physical health drugs and are non-preferred. All agents in the sleep-wake medication class require prior authorization (PA). **Appendix 1** provides a summary of the PDL status for these medications.

- In August 2025, The Oregon Pharmacy and Therapeutics Committee recommended that requests for modafinil or armodafinil be automatically approved when prescribed for members with narcolepsy at a dose at or below 200 mg of modafinil or 250 mg of armodafinil daily.

Background:

Excessive daytime sleepiness is the inability to remain awake and alert during typical hours of wakefulness. It is estimated that anywhere from 3% to 33% of people experience some form of EDS.[12] Disruptions in a person's typical sleep/wake cycle has the potential to hinder academic or professional performance, impact physical and psychological health, and lead to a reduced quality of life.[13] Persistent somnolence or sleep attacks may also increase public health risk due to work injuries or motor vehicle accidents.[14,15] There are a number of sleep conditions that may contribute to EDS. Many of the agents that promote wakefulness are FDA-approved for the treatment EDS due to at least one of the following conditions: narcolepsy, OSA, or shift work disorder.[16] These agents work through a variety of mechanisms many of which are not fully understood.[16] Although some of these agents are first line therapies for their respective indications, adverse effect profiles must be considered with use in certain populations such as in children, in people 65 and older years of age, and in pregnancy.[16] Although several amphetamine-based products are indicated for the treatment of EDS conditions, they will not be covered in this review.

Narcolepsy

Central disorders of hypersomnolence include conditions that are characterized by chronic, severe daytime sleepiness despite the patient getting adequate quality and timing of nocturnal sleep.[17] Narcolepsy is a central hypersomnia disorder that may be categorized into 2 types based on symptoms.[18] Narcolepsy Type 1 is marked by the presence of cataplexy, which is a sudden loss in muscle tone triggered by strong emotions but no loss of consciousness.[19] It has a prevalence of roughly 0.05% in the United States and Europe and affects males and female equally.[20] Type 2 narcolepsy does not show signs of cataplexy.[18] Patients with narcolepsy type 1 have very low levels (≤ 110 picograms per milliliter [pg/mL]) of the neuropeptide orexin A in the cerebrospinal fluid while those with narcolepsy type 2 have normal levels of orexin A.[18] The prevalence of narcolepsy is roughly 30 to 40 cases per 100,000 individuals in White and African American populations, respectively.[21] The etiology of narcolepsy is unclear but type 1 disease is thought to be caused by loss of hypocretin-producing neurons in the hypothalamus.[22] Besides deficient orexin signaling, it is thought that narcolepsy may involve other genetic and autoimmune factors.[23,24] A diagnosis of narcolepsy is typically based on results from a polysomnography (PSG) and multiple sleep latency test (MSLT).[3] The MSLT is a series of five, 20-minute opportunities for naps spaced by 2-hour intervals performed the day after a PSG, and it measures the time it takes to enter REM sleep.[25]

Idiopathic Hypersomnia

Idiopathic hypersomnia is another central disorder of hypersomnolence that results in EDS.[26] Although idiopathic hypersomnia does not have an identified cause, it is defined as daily periods of irrepressible need to sleep, sleep lapses, or drowsiness for at least 3 months without evidence of narcolepsy after sleep lab testing.[27,28] The pathophysiology of idiopathic hypersomnia remains unclear but has been hypothesized to involve circadian mechanisms or increased activation of gamma-aminobutyric acid type A ($GABA_A$) receptors.[27,28] Patients with idiopathic hypersomnia may sleep for long periods at night yet have a sense of inadequate sleep and have extreme difficulty in awakening.[26,27] As with narcolepsy, a diagnosis of idiopathic hypersomnia can be made with PSG and MSLT. It is estimated that the prevalence of idiopathic hypersomnia is 0.002%-0.01% with a mean age of onset between 16-21 years of age.[16,29]

Obstructive Sleep Apnea

Sleep-related breathing disorders such as OSA also cause EDS.[30,31] In OSA, the upper airways are obstructed during sleep which reduces airflow, leading to a fragmented sleep with intermittent hypoxia, hypercapnia, and frequent awakenings.[32] Roughly 2-4% of men and 1-2% of women are reported to experience OSA with an increased prevalence in patients with obesity or history of stroke.[33] Patients with OSA report EDS as well as fatigue, headaches, decreased cognitive ability, and mood disturbances including depression.[33,34] Risk factors for OSA include obesity (Body Mass Index [BMI] $\geq$30 kg/m^2), male gender, and older age.[34] If left untreated, OSA increases the risk for major cardiovascular events, traffic accidents, and increased mortality.[35] OSA is typically diagnosed by PSG with an obstructive respiratory disturbance index (RDI) >5 and <15 events per hour along with symptoms such as sleepiness or fatigue that lead to an impaired sleep-related quality of life.[35-37]

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders are sleep disruptions caused by misalignment of a person's internal circadian rhythm and the external environment.[38] The primary cause of the disorder may be internal or external.[38] 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.[38,39] Intrinsic circadian rhythm sleep-wake disorders are typically defined based on the timing of sleep and wake symptoms.[38,39] Common intrinsic disorders include delayed sleep phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, and non-24-hour sleep-wake syndrome.[38,39] Intrinsic circadian rhythm sleep-wake disorders are typically defined based on the timing of sleep and wake symptoms and diagnosed based on clinical history, sleep logs and actigraphy.[38,39] Extrinsic circadian rhythm sleep-wake disorders are caused by environmental disruptions such as those observed with shift work and jet lag.[38,39] The diagnostic criteria for circadian rhythm sleep-wake disorders include recurrent symptoms of insomnia, sleepiness (or both) caused by misalignment of the endogenous circadian rhythm and the individual's external environment or schedule.[38,39]

The goals of therapy for EDS depend on the primary driver of the sleep-wake condition.[3] For narcolepsy, treatment goals are designed to promote maximal alertness and functioning during waking hours, especially during crucial periods of the day when it is most important (e.g. work, school, home, etc.).[3,18] Besides wakefulness, it is also crucial that patients are able to control symptoms that may reduce quality of life (e.g. cataplexy, hypnagogic hallucinations, and sleep paralysis).[3,18] First-line therapies for narcolepsy are typically stimulant-based medications.[3,18] For EDS secondary to OSA, continuous positive airway pressure (CPAP) is considered the gold-standard therapy because it addresses the underlying cause of obstructed airways.[35,36] With breathing devices such as CPAP, efficacy is dependent upon adherence and cumulative hours of use.[35-37] Studies have demonstrated that nightly CPAP application should be for at least 4 hours and use for at least 70% of the nights to be effective.[37] Stimulant-based pharmacotherapy (e.g. methylphenidate, dextroamphetamine, amphetamine/dextroamphetamine, modafinil, etc.) may be used as adjunct therapy for symptom control but should not be the primary therapy.[35,36] Treatment recommendations for OSA include weight reduction for overweight patients, correction of positional apnea issues, and CPAP/mandibular advancement devices to reduce the apneic episodes and improve sleep quality.[30,40,41] Treatment for circadian rhythm sleep-wake disorders aims to realign the endogenous sleep-wake cycle with the desired external schedule to improve daytime functioning.[38,39] Common outcomes that have been assessed 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.[38,39] There are no well-established standards for minimum clinically important differences in these outcomes for people with circadian rhythm sleep-wake disorders.[38,39]

Modafinil and armodafinil are both FDA-approved to treat excessive somnolence associated with narcolepsy, as adjunct therapy for patients with OSA being treated with CPAP, and for shift work sleep disorder.[42,43] The Oregon Health Plan currently funds treatment of OSA and narcolepsy but does not fund treatment of shift work disorder. Treatment with modafinil and armodafinil (the R enantiomer of modafinil) elicit changes in feelings, mood, perception, and thinking that are commonly observed in central nervous system stimulants but differ from the sympathomimetics in pharmacology.[3] Modafinil and armodafinil stimulate

specific brain regions rather than broadly throughout the brain.[3,18] They do not appear to bind to most of the major brain receptors (e.g. norepinephrine, serotonin, dopamine, gamma-aminobutyric acid, adenosine, histamine 3, melatonin, or benzodiazepine) which may result in less potential risk of dependence or abuse.[18,44] Modafinil and armodafinil are reported to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA, but they do not treat the underlying airway obstruction in OSA.[45] 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. The exact mechanism by which modafinil and armodafinil produce their actions are unknown.[42,43] Common adverse effects reported for modafinil and armodafinil are headache and nausea.[42,43] There is research to suggest that modafinil may be associated with congenital malformations when used in pregnancy.[46-50] Reports of potential fetal harm has prompted many worldwide regulatory agencies and guidelines to recommend that the product not be used in women who are pregnant, are planning to be pregnant, or are breastfeeding.[46-50] Both modafinil and armodafinil are on the FDA's List of Pregnancy Exposure Registries.[46]

Solriamfetol is a non-stimulant medication approved for use in the treatment of sleepiness associated with narcolepsy or obstructive sleep apnea.[51] It is a selective dopamine and norepinephrine reuptake inhibitor with wake promoting effects.[51,52] Solriamfetol was approved based on the results of one phase II trial and 4 phase III clinical trials in patients with narcolepsy or OSA.[53] Compared to placebo at 12 weeks, solriamfetol was associated with improvement in sleep latency (measured by the maintenance of wakefulness test [MWT]) and improved ESS scores in patients with narcolepsy.[51] In patients with OSA, solriamfetol also reported improvements in ESS scores compared to placebo at 12 weeks.[53] However, there was no data to compare solriamfetol to other treatments for narcolepsy or OSA.[54] Whether the observed changes in ESS score or MWT correlate to actual changes in functional status, quality of life, occupation, or social life is unknown. In the trials, solriamfetol use was associated with increases in blood pressure and heart rate which prompted the FDA to recommend monitoring patients for these symptoms during therapy.[51,53] The FDA also recommends cautious use of solriamfetol in patients with acute of untreated psychiatric conditions due psychiatric adverse events observed in the trials (e.g. anorexia, anxiety/nervousness, insomnia, irritability).[51,53]

Pitolisant is an histamine ($H_{3)}$ receptor antagonist/inverse agonist and is FDA-approved to treat cataplexy associated with narcolepsy in adults and for EDS associated with narcolepsy in patients ages 6 through adulthood.[8] It is a non-traditional stimulant thought to promote wakefulness through release of histamine into the central nervous system (CNS) and also by stimulating the release of dopamine, norepinephrine, and acetylcholine in the cerebral cortex.[55-57] Pitolisant received approval based on statistically significant ESS improvements in placebo-controlled studies of 7 to 8 weeks duration.[8] Adverse effects included headache, nausea, decreased appetite, insomnia, and anxiety.[8] Pitolisant is contraindicated in patients with severe hepatic impairment and patients with hepatic or renal impairment should be monitored due to the risk of QT interval prolongation.[8] Some studies have reported that pitolisant remains safe and well tolerated for up to 12 months.[57]

Sodium oxybate is a gamma-aminobutyric acid (GABA) derivative that acts as an inhibitory chemical transmitter in the brain.[7,9] It is approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness due to narcolepsy in patients aged 7 years and older and for idiopathic hypersomnia in adults.[7] The exact mechanism by which sodium oxybate exerts its effects in patients with narcolepsy is largely unclear but is thought to prevent release of the neurotransmitters GABA, glutamate, and dopamine.[7,9,59] Studies with sodium oxybate have reported decreases in the severity and frequency of narcolepsy symptoms including decreased frequency of nocturnal awakenings and dose-dependent increases in the duration of stage 3 and 4 sleep.[58-60] Widespread use of the agent has been limited by significant adverse effects and potential for drug interactions.[59,61] Sodium oxybate, the active moiety in both FDA-approved drug products, is currently available only through the Xyrem® and Xywav® REMS Program due to risk of CNS depression and potential for abuse/misuse.[7,9]

The indications for the FDA-approved agents from the Sleep-Wake PDL class are summarized in **Table 1.**

Table 1. FDA-approved Indications of Drug Agents from the Sleep Wake PDL Class.

Condition	Modafinil (PROVIGIL)	Armodafinil (NUVIGIL)	Pitolisant (WAKIX)	Solriamfetol (SUNOSI)	Sodium oxybate (XYREM, LUMRYZ)	Sodium-, calcium-, magnesium-, and potassium oxybate (XYWAV)
Cataplexy in Narcolepsy	-	-	Adults	-	7 years of age and older	7 years of age and older
EDS in Narcolepsy	Adults	Adults	6 years of age through Adults	Adults	7 years of age and older	7 years of age and older
EDS in OSA	Adults	Adults	-	Adults	-	-
Shift Work Disorder	Adults	Adults	-	-	-	-
Idiopathic hypersomnia	-	-	-	-	-	Adults

Abbreviations: EDS = excessive daytime sleepiness; OSA = obstructive sleep apnea

There is limited evidence available to evaluate the effectiveness of combination therapy among sleep-wake agents.[3,58] There is some data to suggest that sodium oxybate plus modafinil may be more effective than either drug alone, but their combined use has not been recognized by current guidelines.[3,58] Representatives from this drug class have been used as a second line options or as adjunct therapies for depressive episodes in major depressive disorder (MDD), bipolar depression, and treatment-resistant depression (TRD).[62-64] Wakefulness promoting agents have also been studied in other conditions such as treatment of fatigue related to neurologic disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome), for cognitive enhancement, and for attention deficit hyperactivity disorder (ADHD).[2,66-69] There is generally insufficient evidence to support off-label use of non-traditional stimulants such as modafinil for improvement in clinically important health outcomes such as wakefulness or executive functioning.[67] With the vast range of indications and adverse-effect profiles, effective disease management necessitates consideration of evidence based practices as well as individual patient needs and preferences to ensure the best possible outcomes.[3,12,71]

Bipolar Depression and Major Depressive Disorder

Modafinil and armodafinil have been studied as adjunctive treatment for bipolar depression.[62] Several trials have suggested that modafinil 200 mg/day and armodafinil 150 mg/day are more effective than placebo for symptom improvement (e.g. feelings of despair, hypersomnia, fatigue, psychomotor agitation, etc.) however, others were unable to demonstrate a statistically significant difference.[62] Overall, the magnitude of benefit for either agent was minimal.[62] Some trials with armodafinil reported a response rate (reduction of baseline symptoms $\geq$50%) as low as 1% and high as 10% better than placebo.[63] Discontinuation rates due to adverse effects appear to be comparable for both drugs versus placebo.[62,63] Most of the studies were relatively short (6 to 8 weeks) therefore the long-term treatment effects are unclear.[62,63] Fatigue and excessive sleepiness are frequently reported in patients with MDD who are already on an antidepressant.[62,63] Use of modafinil has been reported as useful adjunct therapy for treatment-resistant depression, particularly in patients with a partial response to Selective Serotonin Reuptake Inhibitor (SSRI) monotherapy.[64-66] Modafinil was reported to improve overall clinical condition, and sleepiness/fatigue scores compared to placebo.[62] However, the evidence of benefit was inconsistent and limited by the availability of few published trials most of which were of short duration and overall low quality.[62,63]

Fatigue or Daytime Sleepiness Secondary to: Multiple Sclerosis; Traumatic Brain Injury; Parkinson's Disease

Sleep-wake medications have been used off-label for MS-related fatigue.[71,72] Modafinil 200 mg daily compared to placebo has demonstrated modest benefit in the treatment of fatigue due to MS based on fatigue scales and quality of life measurements.[73,74] However, many of the individual studies reported no difference or inconclusive results and a higher risk of precipitating an adverse event such as insomnia and gastrointestinal disturbances.[73,75,76] For people with traumatic brain injury, improvements in EDS and wakefulness were observed after treatment with 100-200 mg of modafinil once daily.[77] Similarly, armodafinil was reported to improve sleep latency in patients with EDS due to mild or moderate TBI.[78] Both modafinil and armodafinil are recommended by the AASM to treat EDS associated with TBI when benefits outweigh risks.[3] The psychoactive properties of modafinil have been investigated for use in Parkinson's disease (PD)-related fatigue however evidence of benefit is limited and major guidelines suggest its use only in limited circumstances.[3,4,78-79] Reports of increased risk of psychiatric and cardiovascular adverse effects with modafinil may limit its usefulness in people with mental health or cardiovascular disease comorbidities.[71,78]

Attention Deficit Hyperactivity Disorder

Modafinil has been investigated for the treatment of ADHD but study results have been mixed.[80-82] Some studies in children reported statistically significant short-term improvements in core ADHD symptoms compared to placebo, while others have reported no difference compared to more traditional stimulants (e.g. amphetamines, methylphenidate, etc.) or placebo.[67,80,83] Adverse events reported in controlled clinical trials included toxic epidermal necrolysis, Stevens-Johnson syndrome, anxiety, mania, hallucinations, and suicidal ideation.[42] Due to the adverse dermatologic and psychiatric events noted in clinical trials involving children, modafinil has not been FDA approved for use in children for any indication.[42]

Clinical trials have employed a variety of tools to evaluate disease severity and symptom improvement in EDS. Some of the more common validated tools include the Epworth sleepiness scale (ESS) and the maintenance of wakefulness test (MWT).[57,72,85,-87] The ESS is a questionnaire that measures the tendency of a patient to fall asleep in daily situations and is simple for a clinician to administer.[72,85] Patients rate 8 different activities on a 0 (none) to 3 (high) scale with higher scores indicating greater daytime sleepiness (total scores range from 0 to 24).[72,85] An ESS score of greater than or equal to 10 indicates excessive sleepiness which requires further assessment.[72,85] Studies suggest that changes of 20-25% on the ESS (corresponding to approximate differences of 4-6 points) may represent clinically meaningful differences in patients with narcolepsy. [72,85] The ESS is effective for evaluation of most disorders that involve daytime sleepiness. However, the ESS may not adequately assess fatigue as a result of chronic conditions such as MS.[72,85]

The MWT evaluates sleep latency via electroencephalogram (EEG) and requires patients to fight against sleepiness in a soporific (calming) situation. The MWT is designed to evaluate the severity of sleepiness in patients with hypersomnia of central origin (Narcolepsy Type I and II) or OSA.[19,22,23,87] The MWT used in conjunction with the multiple sleep latency test (MSLT) is intended to comprehensively evaluate the patient's ability to fall asleep and their ability to stay awake in a quiet, non-stimulating setting.[86,88] Because it is performed in a laboratory setting, the MWT may not accurately reflect a patients' typical sleep performance.[22,23,87] Both the MSLT and the MWT lack well-defined thresholds for diagnostic and clinical significance.[23,84,87] In patients with narcolepsy, mean sleep latency on the 40-min MWT of less than 8 minutes has been considered abnormal, and values of 8 to 40 minutes are of uncertain significance.[22,87] When used to evaluate the response to a stimulant or CPAP treatment, there are no established thresholds for a change in mean sleep latency.[23,87] Despite apparent limitations, the MWT still provides the strongest support of an individual's ability to stay awake, and the AASM has long endorsed it as an appropriate expectation and standard measurement. [23,87,89]

Other tools are available to help evaluate overall patient improvement and disease severity in patients with sleep wake disorders. The clinical global impression of change scale (CGI-C) and clinical global impression of severity scale (CGI-S) rate improvement based on drug treatment. Both the CGI-C and CGI-S scores range from 1 (very much improved/normal) to 7 (very much worse/severe disease).[90,91] The Functional Outcomes of Sleep Questionnaire (FOSQ) is a tool developed to

measure the effects of EDS on patient QoL.[92] The questionnaire contains 30 items in 5 subscales (activity level, general productivity, sexual relationships, vigilance, and social outcomes).[92] Patients rate the difficulty of performing each task on a scale of 1 (extremely difficult) to 4 (no difficulty) that are summed then averaged to produce a total score range from 5 to 20.[92] A modified 10-question version of the FOSQ (FOSQ-10) has been produced which also has a score range of 5 to 20. [93] The minimally important difference for the FOSQ-10 was reported to range from 1.7 to 2.0 points for adults with EDS and narcolepsy or OSA.[93] Polysomnography may be of use to rule out underlying sleep disorders such as obstructive sleep apnea but does not provide a measure of sleepiness.[94]

In the OHP Fee-for-Service population, use of select medications in the "other stimulants" PDL class (modafinil, armodafinil, and solriamfetol) require prior authorization. Modafinil, armodafinil, and solriamfetol are indicated for the treatment of EDS due to narcolepsy or OSA, while treatment for depression augmentation, cancer-related fatigue, or MS-related fatigue may be approved where there is sufficient evidence of benefit. Currently modafinil, armodafinil, and solriamfetol are "mental health drugs" as defined in OAR 410-141-3855 and are carved out of CCO pharmacy benefits and are reimbursed directly by OHA on a fee-for-service basis. These medications are designated as voluntary non-preferred on the OHP PDL. Sodium oxybate is classified as a physical health drug and is non-preferred. From 1/1/25 to 3/31/25, roughly 90% of requests were for either modafinil or armodafinil. Previous reviews have not identified clinically significant comparative differences in efficacy or harms between agents for narcolepsy including modafinil, armodafinil, solriamfetol, or sodium oxybate. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, incidence of cataplexy attacks, adverse reactions) or off-label dosage consideration to delineate any changes to preferred or non-preferred status.

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) 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.

New Systematic Reviews:
<u>Idiopathic Hypersomnia</u>
A 2021 Cochrane review evaluated medications for daytime sleepiness in people of any age with idiopathic hypersomnia.[1] There were 2 studies identified that investigated treatment with modafinil (n=101) for the diagnoses of primary hypersomnia or hypersomnolence disorder.[1] Data from these trials were judged as having low risk of bias.[1] Both of the included studies used the subjective measure of daytime sleepiness using the ESS as their primary outcome.[1] Secondary outcomes were assessed by the MWT.[1] The modafinil trials were limited by their relatively small size and short duration (3 weeks), so the long-term efficacy and safety of these treatments for daytime sleepiness in individuals with idiopathic hypersomnia is unclear.[1] The small study size also limited the authors' ability to identify rare but serious adverse events.[1] At 3 weeks, modafinil demonstrated a statistically significant improvement in subjective sleepiness compared to placebo based on a lower ESS score of 5.08 points (95% CI 3.01 to 7.16; 2 studies; high-certainty evidence).[1] There was also high-certainty evidence modafinil resulted in a significantly longer mean sleep latency at week 3 than did placebo, by 4.74 minutes (95% CI 2.46 to 7.01 minutes longer).[1] Pooled data showed no

statistically significant differences between groups in adverse event rates, although both studies reported that modafinil treatment compared to placebo resulted in higher rates of headache (26.4% vs 3.3% and 17.6% vs 8.1%, respectively) and gastrointestinal symptoms (19.8% vs 6.6% and 8.8% vs 0%, respectively).[1]

Fatigue in Multiple Sclerosis

A 2024 systematic review evaluated modafinil in the treatment of fatigue in MS.[2] Seven RCTs were included in the review (n=590).[2] The majority of patients were female (71%) and had a diagnosis of relapsing-remitting MS.[2] Pharmacologic treatments included modafinil 200 mg up to 400 mg daily.[2] Primary outcomes included Score on the Modified form of the Fatigue Impact Scale (MFIS), quality of life as measured by various scales (e.g. Short Form 36 Physical Component Summary, Hamburg QoL Questionnaire, etc.), and adverse events (e.g. nausea, insomnia, vomiting, etc.).[2] Secondary outcomes assessed were the score on the ESS and the Fatigue Severity Scale (FSS).[2] The duration of treatment ranged from 2 to 8 weeks.[2] Most RCTs of pharmacologic interventions were evaluated as having moderate risk of bias.[2] Major evidence limitations were attrition bias, publication bias, and heterogeneity of dosing. Treatment with modafinil led to a statistically significant reduction in fatigue compared with placebo, as measured by MFIS (MD = −4.42 [95% CI −8.01 to −0.84]; p=0.02; 5 studies] and modest improvement in ESS scores (MD = −0.87 [95% CI −1.64 to −0.10]; p=0.03; 3 studies).[2] The clinical significance of a less than one-point change on the ESS is unclear. Post-treatment overall physical QoL scores were higher after modafinil treatment compared to placebo (SMD = 0.27 [95% CI 0.07 to 0.46]; p=0.007; 4 studies).[2] Patients treated with modafinil had a higher risk of an adverse event compared to placebo (RR = 1.30 [95% CI 1.03 to 1.66]; p=0.03; 4 studies).[2] The most commonly reported adverse events were gastrointestinal disturbances and insomnia.[2]

After review, 8 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

American Academy of Sleep Medicine

In 2021, the AASM published updated guidelines for the treatment of central disorders of hypersomnolence.[3] The guideline covers the treatment of narcolepsy, idiopathic hypersomnia, and hypersomnia due to medical conditions.[3] Trials were included in the systematic review if they met all criteria such as a hypersomnia diagnosis, outcome of interest (e.g. cataplexy, EDS, fatigue, QoL, etc.) and intervention study type.[3] There were no recommendations given for optimal treatment in pregnant and lactating women.[3] Cost differences, cost-effectiveness, or cost:benefit ratios were not assessed by the guideline committee.[3] Pharmacological recommendations were given either a "strong" (one that clinicians should follow for almost all patients) or "conditional" (lower degree of certainty in appropriateness of the strategy for all patients).[3] Conditional recommendations were based on lower quality evidence.[3] **Table 2** summarizes the relevant pharmacologic recommendations made by the committee.

Table 2. Sleep-Wake Medication Class: Treatment Recommendations from American Academy of Sleep Medicine (modified)[3]

Drug	**Condition or Disorder**					
	Narcolepsy (adults)	Narcolepsy (Pediatrics)	Idiopathic Hypersomnia	Hypersomnia of Parkinson's Disease	Hypersomnia of Multiple Sclerosis	Hypersomnia Secondary to Traumatic Brain Injury
Modafinil	STRONG	CONDITIONAL	STRONG	CONDITIONAL	CONDITIONAL	CONDITIONAL
Armodafinil	CONDITIONAL	-	-	-	-	CONDITIONAL

Sodium oxybate	STRONG	CONDITIONAL	CONDITIONAL	CONDITIONAL	-	-
Pitolisant	STRONG	-	CONDITIONAL	-	-	-
Solriamfetol	STRONG	-	-	-	-	-

NICE – Updated Guidance[4,5]

NICE updated their recommendations for management of PD symptoms and MS in adults. The following table summarizes the key recommendations that involve sleep-wake agents. The NICE recommendations addressed modafinil use and are summarized in **Table 3.**

Table 3. Sleep-Wake Agents for Parkinson's Disease and Multiple Sclerosis

Drug	Year	Disease/Population	Symptom	Recommendation	Warning/Precaution
Modafinil	2017	Parkinson's disease in adults	Daytime Sleepiness	Consider only if a detailed sleep history has excluded reversible pharmacological and physical causes.	Not to be used if planning to become pregnant or during pregnancy or due to risk of malformations. Women of childbearing potential must use effective contraception during treatment and for 2 months after stopping drug. Use an alternate form of birth control (reduces effectiveness of steroidal [hormonal] contraceptives).
	2022	Multiple sclerosis in adults: management	Fatigue	Consider patient needs, priorities, and preferences. Assess potential risks, benefits, and safety concerns. Use the lowest effective dose.	

Department of Veterans Affairs and Department of Defense: Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea[6]

In 2019 the VA/DoD convened a workgroup to update guidance for the management of chronic insomnia and OSA.[6] Literature was reviewed through May 2018 to support the revised recommendations.[6] Pharmacologic agents for the treatment of hypersomnia due to OSA were included in the updated clinical practice guideline.[6] Drug therapy research included armodafinil, methylphenidate, modafinil, solriamfetol, pitolisant, and sodium oxybate.[6] Based on 4 systematic reviews, there was moderate-quality evidence to suggest that modafinil and armodafinil improve the critical outcomes of sleepiness and quality of life in patients with hypersomnia due to OSA but low-quality evidence of no difference in serious adverse events between the agents or placebo.[6] Solriamfetol was found to improve sleepiness (moderate-quality evidence) and quality of life (high-quality evidence).[6] There was no significant difference in serious adverse events between solriamfetol and placebo (moderate-quality evidence).[6] Recommendations for pitolisant were not included due to lack of FDA approval for treatment of residual daytime sleepiness in patients with OSA.[6] Based on the review, there was a weak recommendation for the addition of modafinil, armodafinil, or solriamfetol to treat OSA-related residual excessive daytime sleepiness in patients optimally treated with sufficient primary therapies (e.g. mandibular advancement devices, positive airway pressure [PAP], etc.).[6]

After review, 2 guidelines were excluded due to poor quality.

New Formulations or Indications:
New Indication – October 2018: XYREM (sodium oxybate) oral solution received expanded approval for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.[7] Prior to this approval, sodium oxybate was FDA-approved for the treatment of cataplexy in narcolepsy or EDS in narcolepsy in adults 18 years of age and older.[7]

New Indication – October 2020: WAKIX (pitolisant) received expanded approval for the treatment of EDS or cataplexy in adult patients with narcolepsy.[8]

New Indication – August 2021: XYWAV (sodium oxybate) received expanded approval for the treatment of idiopathic hypersomnia (IH) in adults.[9] Prior to this approval, XYWAV was approved for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy.[9]

New Formulation – May 2023: Lumryz (sodium oxybate) extended-release oral suspension received FDA approval for the treatment of cataplexy or EDS in adults with narcolepsy.[10]

New Indication- June 2024: WAKIX received expanded approval for treatment of EDS in pediatric patients 6 years of age and older with narcolepsy. Prior to this approval, pitolisant was FDA-approved for the treatment of EDS in adult patients with narcolepsy.[8]

New Indication- September 2024: LUMRYZ (sodium oxybate) received expanded approval for the treatment of narcolepsy in patients 7 years and older.[11]

A summary of updated FDA-approved indications for the sleep-wake medications PDL class is provided in **Table 4.**

Table 4. Description of new FDA Safety Alerts[7-11]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
pitolisant	WAKIX	6/24	Adverse Reactions	**Most Common Adverse Reactions** In the placebo-controlled phase of the study, the most common adverse reactions (occurring in ≥5% of patients and greater than the rate of placebo) with the use of WAKIX were headache (19%) and insomnia (7%).
			Use in Special Populations	**Pediatric Use** The safety and effectiveness of WAKIX have been established for the treatment of excessive daytime sleepiness in pediatric patients 6 years of age and older with narcolepsy. Use of WAKIX in this age group is supported by one adequate

				and well-controlled study in 110 pediatric patients with narcolepsy ages 6 to less than 18 years of age. The safety and effectiveness of WAKIX have not been established for treatment of excessive daytime sleepiness in pediatric patients less than 6 years of age with narcolepsy. The safety and effectiveness of WAKIX have not been established for treatment of cataplexy in pediatric patients with narcolepsy. **Juvenile Animal Toxicity Data** In a juvenile animal study, male and female rats were administered pitolisant at 9, 21, or 48 mg/kg/day by oral gavage from postnatal day (PND) 7 to PND 70. Mortality occurred at the highest dose of 48 mg/kg/day; however, death was primarily related to aspiration/inhalation of food material. No adverse effects on growth and development up to the high dose were observed; however, plasma exposures at this dose were lower than those predicted to occur in pediatric patients at the maximum recommended human dose (MRHD) of 35.6 mg due to low oral bioavailability in juvenile rats. In a second juvenile animal study, male and female rats were administered pitolisant at 15 or 30 mg/kg/day or 30 mg/kg/twice daily (60 mg/kg/day) by intraperitoneal injection from PND 7 to PND 70. Mortality and convulsions were observed at the top two doses of 30 and 60 mg/kg/day. Similar findings of convulsions and mortality were also observed in studies in adult rats at comparable doses. The no observed adverse effect level (NOAEL) is 15 mg/kg/day in juvenile animals administered pitolisant by intraperitoneal injection, which corresponds to plasma exposures that are approximately 4 times and 1 time the predicted pediatric exposures at the MRHD of 35.6 mg, based on Cmax and AUC, respectively. **Renal Impairment** Dosage adjustment of WAKIX is recommended in patients with eGFR <60 mL/minute/1.73 m^2
pitolisant	WAKIX	12/22	Use in Specific Populations	**Lactation** Risk Summary

				The transfer of pitolisant into breastmilk is low based on data from a lactation study. The mean infant dose was 0.009 mg/day, and the relative infant dose was less than 1% of the maternal weight-adjusted dose. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WAKIX and any potential adverse effects on the breastfed infant from WAKIX or from the underlying maternal condition. Data An open-label study in 8 healthy lactating women who were 11 to 96 weeks post-partum evaluated the concentration of pitolisant in breast milk samples collected over 24 hours and serum samples collected over 120 hours after a single dose administration of 35.6 mg of pitolisant. Pitolisant was present in breast milk with a mean Cmax of 47.5 ng/mL, while the mean Cmax of pitolisant in serum was 61.4 ng/mL. Following a single dose of pitolisant 35.6 mg, approximately 50% of the amount of pitolisant measured in breast milk occurred during the first 4 hours post dose. Based on single dose data, the mean infant dosage of pitolisant was calculated to be 0.009 mg/day, which represented a mean of 0.564% of the maternal dose received.
solriamfetol	SUNOSI	6/23	Use in Specific Populations	**Lactation** Available data from a lactation study in 6 women indicate that solriamfetol is present in human milk. The daily infant dose is 0.112 mg/kg (based on nominal infant weight of 6 kg). Monitor infants exposed to SUNOSI for signs of agitation, insomnia, and reduced weight gain. Data A single-dose milk and plasma lactation study was conducted in 6 healthy adult lactating women who were between 10 days and 52 weeks postpartum and were administered a single oral 150 mg dose of SUNOSI. The cumulative median amount excreted in breast milk was 0.67 mg over 72 hours, which is about 5.5% of the maternal dose on a weight-adjusted basis. Of the total amount of solriamfetol excreted in breast milk over 72 hours, approximately 78% and 98% were excreted by 8 and 24 hours, respectively, with an apparent mean elimination half-life in breast milk of about 5 hours.

solriamfetol	SUNOSI	6/23	Adverse Reactions	**Postmarketing Experience** Immune system disorders [reported]: Hypersensitivity (rash erythematous, rash [unspecified], and urticaria).
Calcium oxybate; magnesium oxybate; potassium oxybate; sodium oxybate	XYWAV	8/21	Warnings and Precautions	**Respiratory Depression and Sleep-Disordered Breathing** Prescribers should be aware that increased central apneas and clinically relevant oxygen desaturation events have been observed with sodium oxybate administration in adult and pediatric patients. **Depression and Suicidality** In Study 2, depression and depressed mood were reported in 1 patient (1%) and in 5 patients (3%), respectively, of patients treated with XYWAV, all of whom continued XYWAV treatment. **Other Behavioral or Psychiatric Adverse Reactions** In Study 2, confusion occurred in 3% of patients treated with XYWAV, and anxiety occurred in 16% patients treated with XYWAV. One patient experienced visual hallucinations which led to discontinuation of XYWAV. **Parasomnias** In Study 2, parasomnias, including sleepwalking, were reported in 5% of patients treated with XYWAV.
			Use in Specific Populations	**Pediatric Use** Narcolepsy Safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients below the age of 7 years have not been established. Idiopathic Hypersomnia Safety and effectiveness of XYWAV for the treatment of idiopathic hypersomnia in pediatric patients have not been established.
Sodium oxybate	XYREM (label also includes information	2/21	Warnings and Precautions	**Central Nervous System Depression** Clinically significant respiratory depression and obtundation has occurred in adult patients taking sodium oxybate (same active moiety as XYWAV) at recommended doses in clinical trials and may occur in patients treated with XYWAV at recommended doses.

	regarding XYWAV)			**Abuse and Misuse** The active moiety of XYWAV is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. If abuse is suspected, treatment with XYWAV should be discontinued. **XYWAV and XYREM REMS** XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse **Respiratory Depression and Sleep-Disordered Breathing** Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV. **Depression and Suicidality** Depression, and suicidal ideation and behavior can occur in patients treated with XYWAV. In Study 1, depression and depressed mood were reported in 3% and 4%, respectively, of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression, but in most cases, no change in XYWAV treatment was required. **Other Behavioral or Psychiatric Adverse Reactions** Behavioral and psychiatric adverse reactions can occur in patients taking XYWAV. **Parasomnias** Parasomnias can occur in patients taking XYWAV.
			Adverse Reactions Drug interactions	**Clinical Trials Experience** (Extensive changes; please refer to label) **Divalproex Sodium** (an increase in systemic exposure to GHB)

			Pediatric Use	**Use for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older (**supported by evidence from adequate, well-controlled trial)

Randomized Controlled Trials:
A total of 91 citations were manually reviewed from the initial literature search. After review, citations were excluded because of wrong study design (eg, observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trials are summarized in the table below. Full abstracts are included in **Appendix 2**. Evidence from placebo-controlled RCTs may be included for special populations if there is no higher quality evidence available.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Schwitzer et al. 2021[95] DB, PC Duration 12 weeks N=476	1. Solriamfetol (37.5-150 mg/d) + Adherent to Primary OSA Tx* 2. Solriamfetol (37.5-150 mg/d) (nonadherent to Primary OSA Tx) 3. Placebo *=Positive airway pressure (PAP) or other airway therapies (eg, oral appliances, surgical procedures)	Adult participants with EDS in OSA	LS mean differences in MWT sleep latency (minutes) for solriamfetol groups compared to placebo. LS mean differences on ESS score for solriamfetol groups compared to placebo.	<u>MWT Scores</u> (solriamfetol mg/d vs placebo) Adherent to Primary OSA Tx: 37.5 mg: MD 4.8 (95% CI, 0.6-9.0) 75 mg: MD 8.4 (95% CI, 4.3-12.5) 150 mg: MD 10.2 (95% CI, 6.8-13.6) 300 mg: MD 12.5(95% CI, 9.0-15.9) Nonadherent to Primary OSA Tx: 37.5: MD 3.7 (95% CI, –2.0 to 9.4) NS 75 mg: MD 9 (95% CI, 4.4-15.4) 150 mg: MD 11.9 (95% CI, 7.5-16.3) 300 mg: MD 13.5 (95% CI, 8.8-18.3) <u>ESS Score</u> (solriamfetol mg/d vs placebo) Adherent to Primary OSA Tx: 37.5 mg: MD –2.4 (95% CI, –4.2 to –0.5) 75 mg: MD –1.3 (95% CI, –3.1 to 0.5) 150 mg: MD –4.2 (95% CI, –5.7 to –2.7) 300 mg: MD –4.7 (95% CI, –6.1 to –3.2) Nonadherent to Primary OSA Tx: 37.5 mg: MD –0.7 (95% CI, –3.5 to 2.1) NS 75 mg: MD –2.6 (95% CI, –5.4 to 0.1) NS 150 mg: MD –5.0 (95% CI, –7.2 to –2.9)	Trial reported that solriamfetol improved EDS in OSA regardless of primary OSA therapy adherence. Trial reported that primary OSA therapy use was unaffected with solriamfetol. Missing device use data among some participants, could be interpreted as participants staying in the study but discontinuing use of their primary OSA therapy device. Lack of active comparator.

				300 mg: MD –4.6 (95% CI, –7.0 to –2.3)	
Braley et al.[96] CER Duration 12 weeks N=336	1. CBT 2. Modafinil 50-400 mg/d 3. CBT + modafinil 50-400 mg/d	Adult patients with fatigue due to MS	Mean change in MFIS from baseline to week 12	<u>Adjusted MD MFIS change score compared to combination therapy</u> CBT: 1.88 (95% CI –2.21 to 5.96); p=0.37 *Not statistically significant* Modafinil: 1.20 (CI –2.83 to 5.23); p=0.56 *Not statistically significant*	Wide range of flexible dosing once or twice daily based on response. Online assessments may have excluded patients of lower socioeconomic status. Unblinded.
VanDongen et al.[97] RCT, DB, PC Duration 5 weeks N = 59	1. Solriamfetol 150 mg/d 2. Placebo	Adult patients with Excessive Daytime Sleepiness due to OSA and Cognitive Impairment	<u>Primary</u> Mean CFB in average post dose DSST RBANS scores <u>Secondary</u> PGI-S ESS	<u>DSST RBANS scores</u> 1. 6.49 ± 0.65 2. 4.74 ± 0.65 MD: 1.75 (95% CI, 0.46-3.04; P = 0.009; effect size, d = 0.37) <u>Secondary</u> PGI-S MD: -0.29 (95% CI, −0.57 to −0.02; P = 0.034) ESS MD: −2.10 (95% CI, −3.51 to −0.68; P = 0.004)	Low number of participants. Did not include direct comparisons with other WPAs. DSST RBANS lacks a validated minimal clinically important difference.
Dauvilliers et al.[98] DB, PC, RCT Duration 12 weeks N = 268	1. Pitolisant 20 mg/d 2. Placebo	Adult patients with EDS due to OSA and not adhering to CPAP therapy	Primary Mean change in ESS score from baseline to end of intervention	<u>ESS Scores</u> 1. -6.3 2. -3.6 MD: −2.8 (95% CI, −4.0 to −1.5; P < 0.001)	No dose-response assessment was conducted.
Pépin et al.[99] DB, PC, RCT	1. Pitolisant 20 mg/d 2. Placebo	Adult patients with Excessive Daytime Sleepiness	Primary Mean change in ESS score from baseline to end of intervention	<u>ESS Scores</u> 1. -5.5 (95% CI, −6.2 to −4.9) 2. -2.8 (95% CI, −4.3 to −1.2)	Short study duration.

Duration 12 weeks N = 244		due to OSA and refusing or not adhering to CPAP therapy		MD: −2.6 (95% CI, −3.9 to −1.4; P < .001)	CPAP adherence was not assessed systematically during the trial.
Nourbakhsh et al. [100] DB, PC, RCT Duration 12 weeks N=141	1. Amantadine 100 mg twice daily 2. Modafinil 100 mg twice daily 3. Methylphenidate 10 mg twice daily 4. Placebo	Adult patients with MS who reported fatigue	MFIS total measured while taking the highest tolerated dose at 5 weeks.	MFIS Total Score 1. 41.3 2. 39.0 3. 38.6 4. 40.6 MD compared to placebo: 1. 0.7 (95% CI, -2.2 to 3.5) 2. -1.6 (95% CI, -4.5 to 1.2) 3. -2.0 (95% CI, -4.8 to 0.8) *Not Statistically Significant*	Higher proportions of participants reported adverse events (e.g. psychiatric disorders, nervous system disorders, etc.) while taking amantadine (39% patients), modafinil (40%), and methylphenidate (40%) versus 31% for those on placebo.

Abbreviations: CBT=cognitive behavioral therapy; CER = comparative effectiveness research; CFB = change from baseline; CI = confidence interval; CPAP = continuous positive airway pressure; DB = double blind; DSST = Digit Symbol Substitution Test; EDS=excessive daytime sleepiness; ESS=Epworth Sleepiness Scale; LS = least squares; MWT=maintenance of wakefulness test; MD = mean difference; MFIS = Modified Fatigue Impact Scale; MS = multiple sclerosis; NS= Not Statistically Significant; OSA = obstructive sleep apnea; PC = placebo controlled; PGI-S=Patient Global Impression of Severity; RCT = randomized clinical trial; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; tx = treatment; WPA = wake promoting agents

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL	Carve Out
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	
sodium oxybate	LUMRYZ	PACK ER GR	N	
sodium oxybate	LUMRYZ STARTER PACK	GRERPKDSPK	N	
sodium oxybate	SODIUM OXYBATE	SOLUTION	N	
sodium oxybate	XYREM	SOLUTION	N	
sodium,calcium,mag,pot oxybate	XYWAV	SOLUTION	N	

Appendix 2: Abstracts of Comparative Clinical Trials

Schweitzer PK, Mayer G, Rosenberg R, et al. Randomized Controlled Trial of Solriamfetol for Excessive Daytime Sleepiness in OSA: An Analysis of Subgroups Adherent or Nonadherent to OSA Treatment. *Chest.* 2021;160(1):307-318.

Abstract

Background: Solriamfetol, a dopamine-norepinephrine reuptake inhibitor, is approved in the United States to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with OSA (37.5-150 mg/d).

Research question: Does solriamfetol have differential effects on EDS based on adherence to primary OSA therapy and does solriamfetol affect primary OSA therapy use?

Study design and methods: Participants were randomized to 12 weeks of placebo or solriamfetol 37.5, 75, 150, or 300 mg/d (stratified by primary OSA therapy adherence). Coprimary end points were week 12 change from baseline in 40-min Maintenance of Wakefulness Test (MWT) and Epworth Sleepiness Scale (ESS) in the modified intention-to-treat population. Primary OSA therapy use (hours per night, % nights) and safety were evaluated.

Results: At baseline, 324 participants (70.6%) adhered to OSA therapy (positive airway pressure use ≥ 4 h/night on ≥ 70% nights, surgical intervention, or oral appliance use on ≥ 70% nights) and 135 participants (29.4%) did not adhere. Least squares (LS) mean differences from placebo in MWT sleep latency (minutes) in the 37.5-, 75-, 150-, and 300-mg/d groups among adherent participants were 4.8 (95% CI, 0.6-9.0), 8.4 (95% CI, 4.3-12.5), 10.2 (95% CI, 6.8-13.6), and 12.5 (95% CI, 9.0-15.9) and among nonadherent participants were 3.7 (95% CI, -2.0 to 9.4), 9.9 (95% CI, 4.4-15.4), 11.9 (95% CI, 7.5-16.3), and 13.5 (95% CI, 8.8-18.3). On ESS, LS mean differences from placebo in the 37.5-, 75-, 150-, and 300-mg/d groups among adherent participants were -2.4 (95% CI, -4.2 to -0.5), -1.3 (95% CI, -3.1 to 0.5), -4.2 (95% CI, -5.7 to -2.7), and -4.7 (95% CI, -6.1 to -3.2) and among nonadherent participants were -0.7 (95% CI, -3.5 to 2.1), -2.6 (95% CI, -5.4 to 0.1), -5.0 (95% CI, -7.2 to -2.9), and -4.6 (95% CI, -7.0 to -2.3). Common adverse events included headache, nausea, anxiety, decreased appetite, nasopharyngitis, and diarrhea. No clinically meaningful changes were seen in primary OSA therapy use with solriamfetol.

Interpretation: Solriamfetol improved EDS in OSA regardless of primary OSA therapy adherence. Primary OSA therapy use was unaffected with solriamfetol.

Dauvilliers Y, Verbraecken J, Partinen M, et al. Pitolisant for Daytime Sleepiness in Patients with Obstructive Sleep Apnea Who Refuse Continuous Positive Airway Pressure Treatment. A Randomized Trial [published correction appears in *Am J Respir Crit Care Med.* 2020 Jul 1;202(1):154-155.

Abstract

Rationale: Excessive daytime sleepiness is a common disabling symptom in obstructive sleep apnea syndrome.Objectives: To evaluate the efficacy and safety of pitolisant, a selective histamine H3 receptor antagonist with wake-promoting effects, for the treatment of daytime sleepiness in patients with moderate to severe obstructive sleep apnea refusing continuous positive airway pressure treatment.Methods: In an international, multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial, pitolisant was individually titrated at up to 20 mg/d over 12 weeks. The primary endpoint was the change in the Epworth Sleepiness Scale score. Key secondary endpoints were maintenance of wakefulness assessed on the basis of the Oxford Sleep Resistance test, safety, Clinical Global Impression of severity, patient's global opinion, EuroQol quality-of-life questionnaire, and Pichot fatigue questionnaire.Measurements and Main Results: A total of 268 patients with obstructive sleep apnea (75% male; mean age, 52 yr; apnea-hypopnea index, 49/h; baseline sleepiness score, 15.7) were randomized (200 to pitolisant and 68 to placebo) and analyzed on an intention-to-treat basis. The Epworth Sleepiness Scale score was reduced more with pitolisant than with placebo (-2.8; 95% confidence interval, -4.0 to -1.5; $P < 0.001$). Wake maintenance tests were not improved. The Pichot fatigue score was reduced with pitolisant. The overall impact of pitolisant was confirmed by both physicians' and patients' questionnaires. Adverse event incidence, mainly headache, insomnia, nausea, and vertigo, was similar in the pitolisant and placebo groups (29.5% and 25.4%, respectively), with no cardiovascular or other significant safety concerns.Conclusions: Pitolisant significantly reduced self-reported daytime sleepiness and fatigue and improved patient-reported outcomes and physician disease severity assessment in sleepy patients with obstructive sleep apnea refusing or nonadherent to continuous positive airway pressure.

Pépin JL, Georgiev O, Tiholov R, et al. Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. *Chest*. 2021;159(4):1598-1609.

Abstract

Background: Excessive daytime sleepiness (EDS) in individuals with OSA syndrome persisting despite good adherence to CPAP is a disabling condition. Pitolisant is a selective histamine H3-receptor antagonist with wake-promoting effects.

Research question: Is pitolisant effective and safe for reducing daytime sleepiness in individuals with moderate to severe OSA adhering to CPAP treatment but experiencing residual EDS?

Study design and methods: In a multicenter, double-blind, randomized (3:1), placebo-controlled, parallel-design trial, pitolisant was titrated individually at up to 20 mg/day and taken over 12 weeks. The primary end point was change in the Epworth Sleepiness Scale (ESS) score in the intention-to-treat population. Key secondary end points were maintenance of wakefulness assessed by the Oxford Sleep Resistance Test, Clinical Global Impressions scale of severity, the patient's global opinion, EuroQoL quality-of-life questionnaire score, Pichot fatigue questionnaire score, and safety.

Results: Two hundred forty-four OSA participants (82.8% men; mean age, 53.1 years; mean Apnea Hypopnea Index with CPAP, 4.2/h; baseline ESS score, 14.7) were randomized to pitolisant (n = 183) or placebo (n = 61). ESS significantly decreased with pitolisant compared with placebo (-2.6; 95% CI, -3.9 to -1.4; P < .001), and the rate of responders to therapy (ESS ≤ 10 or change in ESS ≥ 3) was significantly higher with pitolisant (71.0% vs 54.1%; P = .013). Adverse event occurrence (mainly headache and insomnia) was higher in the pitolisant group compared with the placebo group (47.0% and 32.8%, respectively; P = .03). No cardiovascular or other significant safety concerns were reported.

Interpretation: Pitolisant used as adjunct to CPAP therapy for OSA with residual sleepiness despite good CPAP adherence significantly reduced subjective and objective sleepiness and improved participant-reported outcomes and physician-reported disease severity.

Braley TJ, Ehde DM, Alschuler KN, et al. Comparative effectiveness of cognitive behavioural therapy, modafinil, and their combination for treating fatigue in multiple sclerosis (COMBO-MS): a randomised, statistician-blinded, parallel-arm trial. *Lancet Neurol*. 2024;23(11):1108-1118.

Abstract

Background: Fatigue is one of the most disabling symptoms reported by people with multiple sclerosis. Although behavioural and pharmacological interventions might be partly beneficial, their combined effects have not been evaluated for multiple sclerosis fatigue, or examined with sufficient consideration of characteristics that might affect treatment response. In this comparative effectiveness research trial, we compared the effectiveness of cognitive behavioural therapy (CBT), modafinil, and their combination for treating multiple sclerosis fatigue.

Methods: This randomised, analyst-blinded, parallel-arm, comparative effectiveness trial was done at two universities in the USA. Adults (aged ≥18 years) with multiple sclerosis and problematic fatigue (Fatigue Severity Scale [FSS] score ≥4) were randomly assigned (1:1:1), using a web-based treatment assignment system with minimisation, to receive CBT, modafinil, or both for 12 weeks. Statisticians were masked to group assignment, but participants, study neurologists, CBT interventionalists, and coordinators were not masked to treatment assignment. The primary outcome was the change in Modified Fatigue Impact Scale (MFIS) from baseline to 12 weeks, assessed using multiple linear regression, adjusted for age, sex, study site, anxiety, pain, baselines MFIS score, and physical activity. Analyses were done by intent to treat. The trial was registered with clinicaltrials.gov, NCT03621761, and is completed.

Findings: Between Nov 15, 2018, and June 2, 2021, 336 participants were randomly assigned treatment (114 assigned to CBT, 114 assigned to modafinil, and 108 assigned to combination therapy). At 12 weeks, CBT (n=103), modafinil (n=107), and combination therapy (n=102) were associated with clinically meaningful within-group MFIS reductions of 15·20 (SD 11·90), 16·90 (15·90), and 17·30 (16·20) points, respectively. Change in MFIS scores from baseline to 12 weeks did not differ between groups: relative to combination therapy, the adjusted total mean difference in MFIS change score was 1·88 (95% CI -2·21 to 5·96) for CBT and

1·20 (-2·83 to 5·23) for modafinil. Most common adverse events for modafinil-containing treatment groups included insomnia (eight [7%] for modafinil and eight [7%] for combination therapy) and anxiety (three [3%] for modafinil and nine [8%] for combination therapy).
Interpretation: Modafinil, CBT, and combination therapy were associated with similar reductions in the effects of multiple sclerosis fatigue at 12 weeks. Combination therapy was not associated with augmented improvement compared with the individual interventions. Further research is needed to determine whether effects of these interventions on multiple sclerosis-related fatigue is influenced by sleep hygiene and sleepiness. No serious adverse events related to the study drug were encountered.

Van Dongen, H et al. Results of the Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-Controlled Study (SHARP) *Chest*, Volume 167, Issue 3, 863 - 875
Abstract
Background
OSA causes episodes of fragmented sleep and intermittent hypoxia and leads to excessive daytime sleepiness (EDS). Deficits in cognitive function are a troublesome symptom in patients with OSA and EDS.
Research Question
How does solriamfetol affect cognitive function in patients with cognitive impairment associated with OSA and EDS?
Study Design and Methods
Solriamfetol's Effect on Cognitive Health in Apnea Participants During a Randomized Placebo-Controlled Study (SHARP) was a phase IV, randomized double-blind placebo-controlled crossover trial. Participants (N = 59) were randomized to receive placebo or solriamfetol (75 mg/d for 3 days, then 150 mg/d) for 2 weeks, with crossover separated by a 1-week washout period. Efficacy measures included the Coding subtest, comparable to the Digit Symbol Substitution Test (DSST), of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the British Columbia Cognitive Complaints Inventory (BC-CCI), the Patient Global Impression of Severity (PGI-S), and the Epworth Sleepiness Scale (ESS). The primary end point was change from baseline in average postdose DSST RBANS scores. Secondary end points were changes from baseline in BC-CCI, PGI-S, ESS, and DSST RBANS scores at 2, 4, 6, and 8 hours' postdose. Safety was monitored by assessment of treatment-emergent adverse events.
Results
Solriamfetol was shown to significantly improve postdose average DSST RBANS scores compared with placebo (P = .009; effect size [Cohen's d], 0.37). When evaluated at each 2-hour time point, cognitive function was significantly improved at 2, 6, and 8 hours after dosing (all, P < .05). During solriamfetol treatment, there were significant improvements in BC-CCI (P = .002; d = 0.45), PGI-S (P = .034; d = 0.29), and ESS (P = .004; d = 0.40) compared with placebo. The most common treatment-emergent adverse events were nausea (7%) and anxiety (3%).
Interpretation
SHARP showed that solriamfetol can improve objective and subjective measures of cognitive function in patients with cognitive impairment associated with OSA and EDS.

Nourbakhsh B, Revirajan N, Morris B, et al. Safety and efficacy of amantadine, modafinil, and methylphenidate for fatigue in multiple sclerosis: a randomised, placebo-controlled, crossover, double-blind trial. *Lancet Neurol.* 2021;20(1):38-48.
Abstract
Background: Methylphenidate, modafinil, and amantadine are commonly prescribed medications for alleviating fatigue in multiple sclerosis; however, the evidence supporting their efficacy is sparse and conflicting. Our goal was to compare the efficacy of these three medications with each other and placebo in patients with multiple sclerosis fatigue.

Methods: In this randomised, placebo-controlled, four-sequence, four-period, crossover, double-blind trial, patients with multiple sclerosis who reported fatigue and had a Modified Fatigue Impact Scale (MFIS) score of more than 33 were recruited at two academic multiple sclerosis centres in the USA. Participants received oral amantadine (up to 100 mg twice daily), modafinil (up to 100 mg twice daily), methylphenidate (up to 10 mg twice daily), or placebo, each given for up to 6 weeks. All patients were intended to receive all four study medications, in turn, in one of four different sequences with 2-week washout periods between medications. A biostatistician prepared a concealed allocation schedule, stratified by site, randomly assigning a sequence of medications in approximately a 1:1:1:1 ratio, in blocks of eight, to a consecutive series of numbers. The statistician and pharmacists had no role in assessing the participants or collecting data, and the participants, caregivers, and assessors were masked to allocation. The primary outcome measure was the MFIS measured while taking the highest tolerated dose at week 5 of each medication period, analysed by use of a linear mixed-effect regression model. This trial is registered with ClinicalTrials.gov, NCT03185065 and is closed.

Findings: Between Oct 4, 2017, and Feb 27, 2019, of 169 patients screened, 141 patients were enrolled and randomly assigned to one of four medication administration sequences: 35 (25%) patients to the amantadine, placebo, modafinil, and methylphenidate sequence; 34 (24%) patients to the placebo, methylphenidate, amantadine, and modafinil sequence; 35 (25%) patients to the modafinil, amantadine, methylphenidate, and placebo sequence; and 37 (26%) patients to the methylphenidate, modafinil, placebo, and amantadine sequence. Data from 136 participants were available for the intention-to-treat analysis of the primary outcome. The estimated mean values of MFIS total scores at baseline and the maximal tolerated dose were as follows: 51·3 (95% CI 49·0-53·6) at baseline, 40·6 (38·2-43·1) with placebo, 41·3 (38·8-43·7) with amantadine, 39·0 (36·6-41·4) with modafinil, and 38·6 (36·2-41·0) with methylphenidate (p=0·20 for the overall medication effect in the linear mixed-effect regression model). As compared with placebo (38 [31%] of 124 patients), higher proportions of participants reported adverse events while taking amantadine (49 [39%] of 127 patients), modafinil (50 [40%] of 125 patients), and methylphenidate (51 [40%] of 129 patients). Three serious adverse events occurred during the study (pulmonary embolism and myocarditis while taking amantadine, and a multiple sclerosis exacerbation requiring hospital admission while taking modafinil).

Interpretation: Amantadine, modafinil, and methylphenidate were not superior to placebo in improving multiple sclerosis fatigue and caused more frequent adverse events. The results of this study do not support an indiscriminate use of amantadine, modafinil, or methylphenidate for the treatment of fatigue in multiple sclerosis.

Appendix 3: Medline Search Strategy

	Ovid MEDLINE(R) ALL 1946 to May 28, 2025	
1	exp Modafinil/	1505
2	armodafinil.mp.	239
3	solriamfetol.mp.	111
4	pitolisant.mp.	221
5	exp Sodium Oxybate/	2007
6	1 or 2 or 3 or 4 or 5	3784
7	exp Fatigue Syndrome, Chronic/	6551
8	exp Multiple Sclerosis/	75274
9	exp Fatigue/	41436
10	exp "Disorders of Excessive Somnolence"/	9013
11	exp Sleep Apnea Syndromes/	46994
12	exp Depression/	170121
13	7 or 8 or 9 or 10 or 11 or 12	338152
14	6 and 13	929
15	limit 14 to yr="2020 -Current"	234
16	limit 15 to (english language and humans)	221
17	limit 16 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 meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	91

Appendix 4: Key Inclusion Criteria

Population	People with central disorders of hypersomnolence (e.g. narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, hypersomnia associated with a psychiatric disorder, hypersomnia due to a medical disorder, circadian rhythm sleep disorders, etc.)
Intervention	Stimulants (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 5: Prior Authorization Criteria

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 diagnosis
- Solriamfetol
- Pitolisant
- All sodium oxybate formulations

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 and/or Evidence-Supported Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)	Solriamfetol (Sunosi™)	Pitolisant (Wakix™)	Sodium Oxybate products
• Excessive daytime sleepiness (EDS) in narcolepsy	X	X	X	X	X
• Cataplexy in narcolepsy	Not FDA approved; insufficient evidence			X	X
• Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP	X	X	X	Not FDA approved; insufficient evidence	
• Bipolar disorder (depressed phase) In combination with conventional medications • Traumatic Brain Injury • Shift work disorder	X	X	Not FDA approved; insufficient evidence		
• Depression augmentation (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue • Parkinson's disease-related fatigue	X	Not FDA approved; insufficient evidence			
• Idiopathic hypersomnia	X	Not FDA approved; insufficient evidence			X (Xywav™)
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence				

ADHD=attention deficit hyperactivity disorder; CPAP=continuous positive airway pressure

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

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
Armodafinil (NUVIGIL)	18 years	250 mg
Modafinil (PROVIGIL)	18 years	200 mg

Solriamfetol (SUNOSI)	18 years	150 mg
Pitolisant (WAKIX)	6 years	17.8 mg (poor CYP2D6 metabolizers)
Sodium oxybate products (XYWAV; XYREM; LUMRYZ)	7 years	9 grams (When administered twice nightly; divided into two doses) 6 grams (When administered once nightly for idiopathic hypersomnia)

Key: g=grams; Kg=kilograms

Table 3. Recommended safety assessments

Modafinil or Armodafinil	Solriamfetol	Pitolisant	Sodium oxybate products
For people of childbearing potential, documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant.	Renal assessment. Dose adjustment is recommended for moderate impairment (EGFR <60 mL/min) and use in end stage renal disease is not recommended.	Renal assessment. Dose adjustment is recommended for moderate renal (EGFR <60 mL/min) and use in end stage renal disease is not recommended.	Patient must be enrolled in the XYWAV and XYREM or LUMRYZ REMS program.
	Recent cardiovascular risk assessment (including blood pressure) within the past 3 months. Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.		Contraindicated for use with sedative hypnotics or with alcohol.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3

Approval Criteria		
3. 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 #4 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
4. Is the requested medication for an FDA-approved age (Table 2) and evidence-supported indication (Table 1)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
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 with a clinically appropriate standard stimulant agent?	**Yes:** Inform prescriber of preferred first-line alternatives (e.g., preferred methylphenidate, amphetamine/dextroamphetamine, armodafinil, modafinil)	**No:** Go to #8
8. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Go to #9	**No:** Go to #11
9. Is the request for modafinil 200 mg twice daily (total daily dose of 400 mg) with documentation of inadequate symptom improvement with lower doses?	**Yes:** Go to #11	**No:** Go to #10

Approval Criteria		
10. 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 #11 Max dose for pitolisant is 35.6 mg daily.	**No:** Pass to RPh. Deny; medical appropriateness.
11. 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 #12 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
12. Is there documentation or provider attestation of recent safety assessments for the requested drug (Table 3)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the request for treatment of narcolepsy or fatigue secondary to major depression (MDD), MS, or cancer? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #14
14. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy)?	**Yes:** Go to #15	**No:** Go to #16
15. Is the patient compliant* with recommended first-line treatments (e.g., CPAP or other primary therapy)? *CPAP compliance = nightly application for at least 4 h and use for at least 70% of the nights.	**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
16. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence to support treatment for excessive daytime sleepiness (EDS) and/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
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) or other covered conditions 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: *10/25; 8/25; 4/23; 10/20; 2/20; 7/19; 03/16; 09/15*
Implementation: *1/1/26; 5/1/23; 11/1/20; 3/1/2020; 8/19/19; 8/16, 1/1/16*