Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Select Wakefulness Promoting Agents

Armodafinil (Nuvigil)

Modafinil (Provigil)

Solriamfetol (Sunosi)

Pitolisant (Wakix)

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Review prepared by:
Valerie Gonzales, Pharm.D., Clinical Pharmacist
Lauren Heath, Pharm.D., MS, BCACP, Clinical Pharmacist
Elena Martinez Alonso, B.Pharm., MSc MTSI, Medical Writer, Sr.
Joanne LaFleur, Pharm.D., MSPH, Associate Professor University of Utah College of Pharmacy

University of Utah College of Pharmacy, Drug Regimen Review Center

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Executive Summary

The four wake-promoting agents (WPAs) reviewed in this report (armodafinil, modafinil, pitolisant, and solriamfetol) have indications for adults that span narcolepsy, a rare disorder; excessive daytime sleepiness (EDS) associated with obstructive sleep apnea (OSA); and shift work-sleep disorder (SWD). The newer agents, solriamfetol and pitolisant, are approved for a subset of these indications, while modafinil and armodafinil cover excessive sleepiness in each condition.[1-4] Solriamfetol is approved for EDS associated with narcolepsy and OSA but does not have approval for SWD. Pitolisant is approved only for narcolepsy but is the single agent of the four WPAs that has been shown to improve cataplexy, a symptom often experienced in narcolepsy, along with excessive daytime sleepiness.

Clinical Guidelines: Updates to US practice guidelines addressing use of WPAs for these conditions are needed since new agents are available. The American Academy of Sleep Medicine (AASM) last published guidelines for the management of narcolepsy and SWD in 2007, and for OSA-related EDS in 2009. A more recent European guideline was published this year for the treatment of narcolepsy.

- First-line pharmacotherapy recommended for improving EDS in **narcolepsy** are modafinil, armodafinil, and sodium oxybate in the 2007 AASM guideline.[5] The 2021 European guideline adds the newer agents, solriamfetol and pitolisant, as first-line options.[6] The European guideline includes pitolisant or sodium oxybate first-line for cataplexy. Second-line options for EDS include methamphetamine- and amphetamine-based stimulants. Combination treatment with a WPA and sodium oxybate or antidepressants may be used to target cataplexy or other symptoms of narcolepsy (eg, sleep paralysis, hypnagogic/hypnopompic hallucinations).[5,6]
- For **SWD**, modafinil was recommended to improve alertness during the nightshift.[7] Other options are scheduled melatonin, hypnotics to promote daytime sleep, and caffeine to improve alertness (but with lower-strength recommendation).[7] The AASM guideline did not consider armodafinil, also approved for SWD, perhaps related to its unavailability at the time of writing.
- WPAs can be used for **OSA-related EDS** after adequate treatment has been provided to the patient to manage the underlying obstruction causing OSA.[8] In the 2009 AASM guideline, modafinil was considered as *adjunctive therapy* to optimized positive airway pressure treatment.[9,10] Currently, experts advise considering WPAs for persistent burdensome EDS symptoms due to OSA (eg, with negative implications on quality of life, work productivity, or safety), *and adjunctive to* adequate treatment for the underlying obstruction.[8] Stimulants such as amphetamines and methylphenidate are not recommended for routine use due to lack of evidence in OSA and since they could pose cardiovascular risk (eg, hypertension, tachycardia) and theoretically greater risk of addiction than other WPAs.[8]

Comparative Evidence: Following a literature search in Medline and Embase, 2 head-to-head randomized controlled trials were identified, both with pitolisant versus modafinil for the treatment of narcolepsy.[11-17] Pitolisant dosed at the higher end of the approved range (17.8 mg to 35.6 mg per day) reduced sleepiness (on the Epworth Sleepiness Scale) similarly to modafinil 100-400 mg per day; yet, pitolisant did not demonstrate non-inferiority to modafinil[18] and modafinil may outperform the lower dosage range of pitolisant (4.5 mg to 17.8 mg per day) for the outcome of sleepiness improvement. There were no significant differences found between pitolisant and modafinil for secondary endpoints related to maintaining wakefulness (in terms of minutes), attention level, and cataplexy rate in either

study.[18] In the single, fully published study of pitolisant versus modafinil**,** there were no changes in cardiovascular parameters in either group.[18] Adverse events reported in 5% or more of patients in the *modafinil arm versus the pitolisant arm* included abdominal pain/discomfort (18% vs. 6%), diarrhea (12% vs. 3%), dizziness (12% vs. 3%), withdrawal symptoms (10% vs. 0%), and anxiety (6% vs. 0%); while headache (35% vs. 18%), and insomnia (10% vs. 0%) occurred in more *pitolisant-treated* patients. No other direct comparative studies were identified for other indications or drug comparisons.

Safety Considerations: Three of the 4 products are schedule IV controlled substances with potential for abuse (pitolisant is the exception).[1,2,4] Yet, abuse potential with these agents is thought to be less than that with traditional stimulants (eg, amphetamine-based and methylphenidate products) that are schedule II substances and have also been used to promote wakefulness for various conditions. The WPAs have potential for drug interactions either related to CYP metabolism for armodafinil, modafinil, and pitolisant; or related to MAOI use for solriamfetol (see Table 7). Prescribers should be cognizant of necessary dose adjustments related to renal impairment for pitolisant and solriamfetol; or hepatic impairment for armodafinil, modafinil, and pitolisant. Pitolisant should be avoided in severe hepatic impairment, and both pitolisant and solriamfetol are not recommended in end-stage renal disease. Of these WPAs, pitolisant has the potential to prolong the QTc interval so ideally should not be used with other QTc prolongating drugs or in patients who have arrhythmia history or risk factors for QTc prolongation.[3]

Intolerability to WPAs may be due to headache or nausea, which are 2 of the more common side effects with these medications. Other less frequent side effects include nervousness, anxiety, dry mouth, decreased appetite, insomnia, and GI symptoms. Patients should be warned of rare but serious hypersensitivity reactions possible with armodafinil/modafinil.[1,2] WPAs as a class should be used cautiously in patients with psychiatric history and dose reduced or discontinued if psychiatric symptoms develop or worsen. Since these agents can slightly increase blood pressure and/or heart rate, particularly modafinil, armodafinil and solriamfetol,[1-4,19,20] patients with a hypertensive history should have blood pressure well-controlled before starting treatment and be monitored for excursions.[1,2]

PDL Consideration: The four WPAs reviewed are not currently on the Utah Medicaid Preferred Drug List (PDL), however, are accessible through a prior authorization if treating FDA-approved indications or the off-label indication of sedation related to multiple sclerosis therapy (for modafinil only). Solriamfetol and pitolisant, require initial trial and failure of armodafinil or modafinil. For the purposes of the PDL, these agents can be considered as similarly efficacious for improving the symptom of excessive sleepiness for their respective indications: armodafinil and modafinil, now generic, cover excessive sleepiness due to OSA, shift-work disorder, and narcolepsy, while the newer brand-name medications are approved for a subset of these conditions. Pitolisant (Wakix) is the only agent of these WPAs with demonstrated efficacy and FDA approval for the symptom of cataplexy. Patients may request pitolisant for this purpose especially if having insufficient relief from other anti-cataplectics used in practice (eg, antidepressants). Providers may request a particular WPA after weighing the different medication indication/safety profiles against patient-specific symptoms and comorbidities (eg, abuse risk, QTc prolongation risk, cardiovascular risk, drug elimination impairments, and drug-drug interactions) and treatment history/failure with other agents.

Introduction

This review covers 4 wake-promoting agents (WPA), armodafinil, modafinil, pitolisant, and solriamfetol, with indications that span narcolepsy, excessive sleepiness associated with obstructive sleep apnea (OSA), and shift-work sleep disorder (SWD).[1-4] In this report, the term WPA will refer solely to these 4 drug entities. Other agents that have some overlapping effects (eg, amphetamine-based or methylphenidate stimulants) or that are used for overlapping indications will be referred to separately. Armodafinil, modafinil, and solriamfetol are schedule IV controlled substances since they can produce some psychoactive or euphoric effects[1,2] or drug-liking effects[4]; pitolisant is a non-controlled product.

Each WPA is indicated for excessive sleepiness associated with narcolepsy, a rare disorder. Pitolisant and solriamfetol, approved in 2019, are newer drug entities than modafinil and armodafinil, initially brought to market more than a decade ago. In addition to excessive sleepiness due to narcolepsy, pitolisant is also indicated for cataplexy, a salient symptom of narcolepsy experienced by at least half of diagnosed individuals.[12,21] The other 3 WPAs are not known or established to be effective for modifying cataplectic symptoms; but, other medications, some off-label such as antidepressants, have been in use for cataplexy and other symptoms of narcolepsy (eg, sleep paralysis, hypnagogic hallucinations) as further discussed on page 10. With the exception of pitolisant, the WPAs (armodafinil, modafinil, and solriamfetol) are also approved for excessive sleepiness related to OSA. They can be used after adequate treatment has been provided to manage the underlying obstruction causing OSA since the WPAs treat the symptom of sleepiness and not the obstruction.[8] Of the 4 WPAs, only armodafinil and modafinil, have approvals for the treatment of excessive sleepiness related to nightshift work.

WPAs reduce excessive sleepiness related to OSA and narcolepsy often assessed in clinical studies by the Epworth Sleepiness Scale (ESS) and Maintenance of Wakefulness Test (MLT).[1-4,18] The ESS score is based on subjective patient response for perceived likelihood of falling asleep during hypothetical daily activities (lower scores reflect less symptom severity),[18] while MWT objectively assess the duration the patient is able to remain awake in the daytime but in a darkened, quiet environment.[4] Regarding SWD, armodafinil and modafinil provide small reductions in sleepiness (per Karolinska Sleepiness Scale, based on subjective response) and increase alertness during the nightshift.[22] **Table 1** provides an overview of the FDA-approved indications for the WPA—each approved for use in adults only.

Table 1. Indicated Disorder [1-4]

Generic (Brand)	For improving wakefulness in adults with **excessive sleepiness**[a,b] associated with the following:		
	Obstructive sleep apnea	**Narcolepsy**	**Shift-work disorder**
Armodafinil (Nuvigil)	✓	✓	✓
Modafinil (Provigil)	✓	✓	✓
Solriamfetol[a] (Sunosi)	✓	✓	
Pitolisant[b] (Wakix)		✓ Also for *cataplexy* symptoms	

[a] The indication for solriamfetol, more specifically, is with respect to excessive *daytime* sleepiness
[b] The indication for pitolisant is for excessive sleepiness *or cataplexy* associated with narcolepsy

In addition to the labeled indication, **Table 2** provides the dosages and dose adjustments recommend for these products per approved labeling.

Table 2. Wakefulness Promoting Agents, Indication and Dosage[1-4]

Generic Name **Brand** and forms (approval year)	**Indication**	**Dosing**
Armodafinil **Nuvigil** oral tablet Generic available • 50 MG, • 150 MG, • 200 MG, • 250 MG (2007)	To improve wakefulness in adults with excessive sleepiness associated with OSA, narcolepsy, or shift work disorder Limitations: Not intended to treat the underlying airway obstruction in OSA	For OSA or Narcolepsy: 150 -250 mg in the morning For SWD: 150 mg, up to once daily about 1 hour prior to the start of the work shift Dose Adjustments: ▪ Severe hepatic impairment: reduce dose ▪ Geriatric Patients: consider lower dosage
Modafinil **Provigil** oral tablet Generic available • 100 MG, • 200 MG (1998)	To improve wakefulness in adults with excessive sleepiness associated with OSA, narcolepsy, or shift work disorder Limitations: Not intended to treat the underlying airway obstruction in OSA	For OSA or Narcolepsy: 200 mg in the morning o Higher doses, up to 400 mg/day, may be tolerable but there is no clear evidence of additional benefit beyond 200 mg/day For SWD: 200 mg, up to once daily about 1 hour prior to the start of the work shift. Dose Adjustments: ▪ Severe hepatic impairment: use a 50% dose reduction ▪ Geriatric Patients: consider lower dosage
Solriamfetol **Sunosi** oral tablet *Brand only* • 75 MG, • 150 MG (2019)	To improve wakefulness in adults with excessive *daytime* sleepiness due to narcolepsy or OSA; initiate after treating underlying airway obstruction in OSA (eg, with continuous positive airway pressure) for at least 1 month and should continue such treatment Limitations: Not intended to treat underlying airway obstruction in OSA	For Narcolepsy: start 75 mg, once daily upon awakening; after 3 days may increase up to 150 mg For OSA: start 37.5 mg once daily upon awakening; after 3 days may increase up to 150 mg o *Avoid taking within 9 hours of planned bedtime* Dose Adjustments: ▪ Moderate renal impairment (eGFR 30-59 mL/min/1.73m^2): Start 37.5 mg/day; may increase to 75mg/day after at least 7 days ▪ Severe renal impairment (eGFR 15-29 mL/min/1.73 m^2): Starting and maximum dose is 37.5mg/day ▪ End stage renal disease (ESRD): avoid use
Pitolisant **Wakix** oral tablet *Brand only* • 4.45 MG, • 17.8 MG (2019)	To treat excessive daytime sleepiness **or** cataplexy in adult patients with narcolepsy	Use 17.8-35.6 mg up to once daily in the morning upon awakening; should titrate as follows: o Week 1, 8.9 mg once daily; Week 2, increase to 17.8mg once daily; Week 3, may increase up to 35.6 mg once daily Dose Adjustments: ▪ Moderate hepatic impairment: Start at 8.9 mg/day; titrate to a maximum of 17.8 mg/day after 14 days

Table 2. Wakefulness Promoting Agents, Indication and Dosage[1-4]

		▪ Contraindicated in severe hepatic impairment ▪ Moderate and severe renal impairment: Start at 8.9mg/day; titrate up to 17.8 mg/day after 7 days ▪ End-stage renal disease: Not recommended ▪ Poor CYP2D6 Metabolizers: Maximum dosage is 17.8mg/day

Methods

Systematic Literature Search

Search strategies were developed for the systematic reviews (SRs) in Ovid-Medline and Embase. Databases were searched up to May 24th of 2021. Strategies in Medline and Embase consisted of keyword phrases and controlled vocabularies such as Medical Subject Headings (MeSH) or Emtree terms. The complete search strategies are available in **Appendix A.** A combination of independently derived filters and a McMaster University filter[23] were used to identify SRs in Ovid-Medline; an independently derived filter was used in Embase for SRs. In Embase, we excluded conference abstracts and limited to English language.

After reviewing pertinent SRs and the dates of their literature searches, a supplemental search to target more recently published RCTs was performed from 2013 onward in OvidMedline regardless of indication; and from 2016 onward in Embase for each indication and from 2013 onward for the shift-work-sleep disorder indication. These years were chosen to supplement the following search dates of pertinent SRs:

- A Cochrane SR addressing the effects of agents for the treatment of excessive sleepiness due to **shift-work sleep disorder** searched for RCT evidence into 2013[22]
- SRs addressing **WPAs** for the treatment of excessive sleepiness in **OSA** searched for RCTs to December 2014 for one and to October 2015 for the other.[24,25] Other SRs focusing on solriamfetol[26-28] had more updated searches into 2020.
- An SR addressing **WPAs** for the treatment of excessive sleepiness in **narcolepsy** searched for RCTs through 2017.[29] Other SRs focusing on solriamfetol[26-28] or pitolisant[30] had more updated searches into 2020.

Publication filters for RCTs were used, obtained from the Cochrane Collaboration Handbook for SRs (for Ovid-Medline)[31] and from the Cochrane website (for Embase).[32]

For treatment guidelines addressing the management of excessive sleepiness due to OSA, SWD, and narcolepsy, we searched the website of the College of Psychiatric and Neurologic Pharmacists which provides a compilation of treatment guidelines for various neurologic disorders: https://cpnp.org/guideline/external/sleep. Additionally, websites for the following organizations were searched:

I. American Academy of Sleep Medicine (AASM): https://aasm.org/clinical-resources/practice-standards/practice-guidelines/
II. American Academy of Neurology (AAN): https://www.aan.com/policy-and-guidelines/guidelines/
III. Guideline Central: https://www.guidelinecentral.com/
IV. American Psychiatric Association (APA): https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

For professional prescribing information (ie, product labeling or package inserts), we searched the drug sponsor's website for each brand product, or websites such as Drugs@FDA and dailymed.nlm.nih.gov.

Screening

Two reviewers independently screened publication titles and abstracts for inclusion. Conflicts were resolved by consensus between reviewers. The full text for all citations receiving 2 inclusion votes were retrieved. The lead author made the final determination for inclusion upon full-text review. **Figure 1** in **Appendix B** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria

For the *Direct-Comparative Evidence* section of the report we included evidence based on randomized controlled trials (RCTs) comparing active arms of treatments listed in Table 1, reporting efficacy or safety outcomes for the treatment of *approved* indications for the WPAs. Direct pair-wise meta-analysis statistical data was sought, while mixed- or indirect-comparative statistical data (ie, network meta-analyses) was excluded.

Disease Overview and Treatment Guidelines

Narcolepsy

Narcolepsy may affect as many as 1 in 2000 persons in the United States and usually persists throughout the patient's lifetime.[21] Despite having disturbed nocturnal sleep (DNS), patients with narcolepsy usually feel well-rested in the morning upon awakening.[21] They become excessively sleepy later, usually with moderate to severe daytime sleepiness for long periods throughout the day. These patients have difficulty staying awake or feeling wakeful as REM sleep intrudes into their daytime activities. Patients may suddenly fall asleep (ie, sleep attack) with or without episodes of sudden transient muscle weakness or paralysis lasting a couple minutes (ie, cataplexy). Cataplexy is typically triggered by strong emotions in affected individuals and occurs in about half to 70% of patients with narcolepsy.[12,21] Other symptoms that occur in narcolepsy may include dream-like hallucinations (HH) when falling asleep (hypnagogic hallucinations) or upon awakening (hypnopompic hallucinations); or muscle paralysis upon awakening (sleep paralysis [SP]). Patients with narcolepsy have abnormal nighttime sleep patterns, entering REM sleep more quickly than people without narcolepsy; but, sleep progresses in a more fragmented pattern.[21]

Narcolepsy can occur in children, adolescents, and adults.[33] In children and adolescents, school performance can suffer along with family and social relationships, placing them at risk for depression. In adults, poor performance in the work setting due to narcoleptic symptoms is associated with lower earning potential and increased psychiatric co-morbidity.[33] It is common for patients to present with symptoms before 18 years of age[12] and often patients experience a delay in diagnosis or misdiagnosis.[33,34]

Narcolepsy can arise from a deficiency of orexin neuropeptides, also called hypocretins, which are known to play an essential role stimulating persistent wakefulness and suppression of REM sleep during the day.[21] Autopsy studies in patients with narcolepsy have found near complete loss of the orexin-producing neurons in the hypothalamus.[21] Some patients, however, may not have orexin deficiency and the underlying etiology may be more obscure. Orexin receptor mutations, traumatic brain injury, or other co-occurring neurologic disorders (eg, tumors or strokes) are possible causes aside from a deficiency of orexin.[21]

The diagnosis of narcolepsy is made according to criteria by the ICSD-3 (International Classification of Sleep Disorders – 3rd edition) published by the American Academy of Sleep Medicine (AASM). Narcolepsy with cataplexy and/or hypocretin-1 deficiency is classified as type 1 narcolepsy. Type 2 narcolepsy is absent of cataplexy; patients may have normal orexin levels and potentially undetermined causes of their condition.[21,35] Polysomnography (PSG) and the multiple sleep latency test (MSLT) are used to help rule out other possible causes.[21] MSLT is a daytime nap study, with five scheduled naps 2-hours apart.[21] MSLT assesses the time to falling asleep which helps objectively inform about the level of sleepiness. A polysomnogram reveals REM sleep dysregulation.[21] Diagnostic criteria from AASM and the DSM-5 are outlined in **Table 3**. Ruoff et al describe that DSM-5 is typically used by mental health and general practitioners, while the ICSD-3 criteria is intended for sleep medicine specialists.[35]

Table 3. Narcolepsy Diagnostic Criteria[35]

American Academy of Sleep Medicine ICSD-3, 2014

Narcolepsy Type 1

- Daily excessive daytime sleepiness for ≥3 months
- AND at least one of the following bullets:
  - Cataplexy and mean sleep latency of ≤8 minute average with ≥2 episodes of REM sleep (ie, SOREMP) on MSLT. An SOREMP of ≤15 min of falling asleep as demonstrated on nocturnal PSG may replace one of the SOREMPs on MSLT
  - CSF hypocretin-1 level of either ≤110 pg/mL (per immunoreactivity assay) or ≤ 1/3rd of the mean value in otherwise healthy subjects

Narcolepsy Type 2

- Daily excessive daytime sleepiness ≥3 months and MSLT findings as in Type 1, but without cataplexy
- CSF hypocretin-1 levels undetermined or are above the type 1 threshold
- Hypersomnolence and/or MSLT findings are not better explained by other causes (eg, sleep insufficiency, OSA, delayed sleep phase disorder, or medication/substance use effect)

DSM-5, American Psychiatric Association 2013

Narcolepsy

- Recurrent irrepressible episodes of the need to sleep or lapses into sleep/napping at least 3 times weekly over the past 3 months
- AND presence of at least one of the following:
  - Cataplexy at least a few times per month characterized as either:
    - "In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking"[35]
    - "In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers"[35]
  - CSF hypocretin-1 levels of either ≤110 pg/mL (per immunoreactivity assay) or ≤ 1/3rd of the mean value in otherwise healthy subjects; however, this is not required in the context of acute brain injury, inflammation, or infection
  - Nocturnal sleep PSG showing REM onset at ≤15 minutes of falling asleep, or an MSLT showing a mean sleep latency of ≤8 minutes and ≥2 SOREMPs

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders; CSF, cerebrospinal fluid; ICSD, International Classification of Sleep Disorders; MSLT, multiple sleep latency test; PSG, polysomnography; SOREMP, sleep-onset REM period

Treatment

The last formal US guidelines for the treatment of narcolepsy were published in 2007 by AASM, so they do not incorporate the newer approved agents for narcolepsy (pitolisant or solriamfetol) into recommendations.[5] These agents were not approved until the following decade. More recently, a European guideline was published in June 2021 from a panel directed by the European Academy of Neurology, European Sleep Research Society, and European Narcolepsy Network.[6]

AASM describes that while modafinil and second-line stimulants such as methylphenidate or amphetamine-based can be used to improve alertness and the feeling of wakefulness due to narcolepsy, they do not treat cataplexy or REM-sleep associated symptoms. Whereas, antidepressants and some anti-cataplectics can be used for purposes of cataplexy but have little effect on daytime alertness. Co-prescribing of 2 or more drug classes may be necessary to target various symptoms. Moreover, combinations of long- and short-acting dosage forms of stimulants may be used for some cases to take advantage of quick onset or long duration of action of different products for tailoring duration or timing of effect to the patient's symptoms.[5] The 2021 European guideline reiterates that modafinil-based agents and solriamfetol are not expected to be useful for reducing cataplexy and there is no strong data supporting their use for other symptoms such as disturbed nocturnal sleep (DNS), sleep paralysis (SP), or hypnagogic/hypnopompic hallucinations (HH). However, pitolisant can be used to treat cataplexy and has some evidence and weak recommended for reducing HH.[6]

In the 2021 European guideline, modafinil, pitolisant, and solriamfetol are among first-line treatment strategies for the management of narcolepsy: each are first-line options for EDS symptom, and pitolisant is also first-line for cataplexy. Moreover, they may be used in combination regimens with other agents (antidepressants or sodium oxybate) that target additional symptoms.[6] In the 2007 AASM guideline, agents recommended for EDS with the highest grade of recommendation were modafinil, armodafinil, and sodium oxybate (Standard level of recommendation[*], 2007 AASM).[5] Methamphetamine- and amphetamine-based stimulants have a lower grade of recommendation since well-designed studies are limited despite their long history of use (Guideline level recommendation*); this is consistent with European guideline. Optional agents for cataplexy or other symptoms (ie, hypnagogic hallucinations [HH], sleep paralysis) are listed in Table 1 (eg, antidepressants, sodium oxybate, or selegeline) but do not include the stimulants or WPAs.

Alongside modafinil and sodium oxybate, a 2017 French Consensus Statement by sleep-medicine specialists, includes pitolisant as an effective treatment for EDS due to type 1 narcolepsy and considers these 3 agents as first-line options.[36] Methylphenidate was considered a second-line option usually after having failed modafinil. Armodafinil and solriamfetol were not approved in France during the writing of the consensus statement.[36]

For children, although modafinil is approved for 18 years or older, the AASM guideline listed this medication as a treatment option for EDS, in addition to methylphenidate.[5,33] In the 2021 European guideline, sodium oxybate is given a strong recommendation for management of EDS and cataplexy, but based on low-quality evidence; and a weak recommendation for other symptoms (eg, SP, HH, DNS) in pediatric narcolepsy. Other options are given weak recommendation for use by the European guideline,

[*] Refer to the bottom of Table 4 on page 14 for a description of the recommendation categories from AASM

due to very low to low quality evidence: methylphenidate, modafinil, and pitolisant for EDS; and antidepressants for cataplexy, SP, or HH.

Table 4 summarizes information from the 2021 European guideline and the 2007 AASM guideline for narcolepsy.

Table 4. Clinical Practice Guidelines for Narcolepsy

European Academy of Neurology (EAN), European Sleep Research Society (ESRS) and European Narcolepsy Network (EU-NN), 2021[6]

Guideline Title: *European guideline and expert statements on the management of narcolepsy in adults and children*

- Treatment goal for most symptomatic treatments is generally to improve the sleep-wake cycle with particular attention to daytime performance and sleepiness; and to reduce rate of cataplexy for applicable to patients
- Tailor therapy to patient-specific symptoms, comorbidities, tolerance, and risk of potential drug interactions
- There is insufficient data from head-to-head studies to compare the efficacy of different drugs

Recommendations in favor for pharmacotherapies based on symptom

Excessive daytime sleepiness (EDS)

Adults:

- Strong recommendation with moderate-quality evidence in support of modafinil, pitolisant, solriamfetol, and sodium oxybate
- Weak recommendation with low-quality evidence supporting use of methylphenidate and amphetamine derivatives

Children:

- Strong recommendation with low-quality evidence in support of sodium oxybate
- Weak recommendation with very low level evidence supporting use of methylphenidate, modafinil, and pitolisant

Cataplexy

Adults:

- Strong recommendation with moderate or low quality evidence in support of sodium oxybate or antidepressants (venlafaxine, and clomipramine), respectfully
- Weak recommendation with moderate-quality evidence supporting use of pitolisant

Children:

- Strong recommendation with low-quality evidence in support of sodium oxybate
- Weak recommendation with very low-quality evidence supporting use of antidepressants

Disturbed nighttime sleep (DNS)

Adults:

- Strong recommendation with moderate-quality evidence in support of sodium oxybate

Children:

- Weak recommendation with no evidence supporting use of sodium oxybate

Sleep paralysis (SP) and hypnagogic/hypnopompic hallucinations (HH)

Adults:

- Weak recommendation with low level evidence supporting use of pitolisant, sodium oxybate, and antidepressants

Children:

- Weak recommendation with very low-quality evidence or no data in support of antidepressants and sodium oxybate respectfully

Treatment Algorithm: the European guideline lays out first-line and second-line strategies depending on the patient's symptoms: (a) EDS as main symptom, (b) EDS with Cataplexy, and (c) EDS with Cataplexy and DNS.

- First-line for scenario (a): modafinil, pitolisant, or solriamfetol
- First-line for scenario (b): pitolisant, sodium oxybate (SXB), or combination therapy with a WPA and antidepressant (venlafaxine or clomipramine) or sodium oxybate
- First-line for scenario (c): sodium oxybate monotherapy, or combination of SXB and/or VEN/CLO plus a WPA; or any WPA, VEN/CLO, and short-term z-drug
- Refer to guideline for second line strategies.

American Academy of Sleep Medicine (AASM), 2007[5]

Guideline Title: *Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin*

Medications recommended for adults:

I. Modafinil/Armodafinil: considered effective for treatment of **daytime sleepiness** due to narcolepsy (Standard)
   - This recommendation seems to also apply to armodafinil, as authors describe a level 1 evidence supporting efficacy of this R-enantiomer of modafinil (with a longer half-life than the S-enantiomer); there are many level 1 studies supporting the use of modafinil
   - Authors also note that Level 1 evidence shows a split dosing strategy (given in the morning and at noon) with modafinil provides better control of daytime sleepiness than a single daily dosing of modafinil.
   - Other potential uses where modafinil may be an effective treatment for daytime sleepiness related to the following (which are off-label uses):
     - Parkinson's disease (Option), myotonic dystrophy (Option)
     - multiple sclerosis (Guideline)
     - idiopathic hypersomnia (with and without long sleep time), recurrent hypersomnia, and hypersomnia due to a medical condition (Option)

II. Sodium oxybate: considered effective for treatment of **cataplexy**, **daytime sleepiness**, and **disrupted sleep** due to narcolepsy (Standard)
   - May also be effective for treatment of hypnagogic hallucinations and sleep paralysis (Option)

III. Other Stimulants: Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate: considered effective for treatment of **daytime sleepiness** due to narcolepsy (Guideline)
   - While these agents have a long history of use/efficacy in clinical practice there is limited evidence regarding the benefit-to-risk ratio which is likely related to limited research funding for generics.
   - The listed stimulants may be effective for daytime sleepiness in idiopathic hypersomnia, recurrent hypersomnia, and hypersomnia due to a medical condition (Option)
   - Methylphenidate may be effective for daytime sleepiness due to myotonic dystrophy (Option)
   - "Combinations of long- and short-acting forms of stimulants may be indicated and effective for some patients (Option)."

Table 4. Clinical Practice Guidelines for Narcolepsy

IV. Tricyclic antidepressants, SSRIs, and venlafaxine: may be effective for **sleep paralysis** and **hypnagogic hallucinations**; can used when benefits outweigh risks (Option, based on anecdotal experience of committee members)

V. Selegiline: may be effective to **cataplexy** and **daytime sleepiness** (Option)

Recommendation for children (Ages 6-15 years old):

I. Modafinil and methylphenidate are considered relatively safe for the treatment of hypersomnias of central origin (Option)
   - "One level 4 open label study showed modafinil was effective in improving sleepiness and was generally well tolerated in 13 children (mean age 11 years) with narcolepsy or idiopathic hypersomnia"

Abbreviations*:* AASM, American Academy of Sleep Medicine*;* CLO, clomipramine*;* DNS, disturbed nocturnal sleep; EDS, excessive daytime sleepiness; SXB, sodium oxybate; VEN, venlafaxine; WPA, wake promoting agent

AASM Recommendation Categories

- **Standard =** high degree of clinical certainty; implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.
- **Guideline =** moderate degree of clinical certainty; implies the use of level 2 evidence or a consensus of level 3 evidence.
- **Option** = uncertain clinical use; implies either inconclusive or conflicting evidence or conflicting expert opinion.

AASM Level of Evidence

- **Level I =** Randomized, well-designed trials with low alpha and beta error, or meta-analyses of randomized controlled trials with homogeneity of results
- **Level II =** Randomized trials with high alpha and beta error, methodologic problems, or high quality cohort studies
- **Level III =** Nonrandomized concurrently controlled studies (case-control studies)

Excessive Daytime Sleepiness Associated with Obstructive Sleep Apnea

In 2013, it was estimated that in the US there are 14% of men and 5% of women who experience at least 5 apnea-hypopnea events per hour at night plus symptoms of daytime sleepiness which meets Medicare criteria for obstructive sleep apnea.[37] Obstructive sleep apnea (OSA) is the most common diagnosis contributing to excessive daytime sleepiness (EDS). EDS increases the risk of motor vehicle crashes by 2-3 times.[38] OSA results from collapse of the upper airway and symptoms include loud snoring, breathing interruption, awakenings from gasping or chocking, daytime sleepiness, and increased sympathetic activity. Diagnosis usually entails demonstration of at least 5 obstructive respiratory events in per hour of sleep (eg, apneas, hypopneas, respiratory effort leading to awakening). In absence of sleep-related symptoms, 15 or more obstructed respiratory events per hour of sleep also meets criteria for diagnosis of OSA.[9]

Patients who are at high risk and who should be screened for OSA include those with obesity, heart failure, atrial fibrillation, refractory hypertension, type 2 diabetes, stroke, nocturnal dysrhythmia, pulmonary hypertension, and high-risk driving populations.[9] High-risk drivers are considered as those with moderate to severe daytime sleepiness and a recent car accident (or a near miss) attributed to sleepiness, fatigue, or inattention. Patients with suspected or confirmed OSA should be asked about patterns of daytime sleepiness, especially occurrences of unintended falling asleep or motor vehicle incidents due to excessive sleepiness.[38]

Treatment

OSA is a chronic disease that requires long-term management.[9] Positive airway pressure (PAP) is a primary treatment for mild to severe OSA. US guidelines recommended PAP versus no therapy, to treat OSA in adults with excessive sleepiness (strong recommendation; 2019)[39] and to reduce the risk of harm in patients at high risk of driving accidents (strong recommendation, moderate quality evidence; 2013).[38] If PAP is intolerable or declined by the patient or insurance, other therapies can be offered depending on severity, symptoms, anatomy, risk factors, and patient preferences (eg, behavioral, oral appliances, or surgical intervention).[9,39]

In the 2009 AASM guideline, modafinil was considered an *adjunctive therapy* to optimized PAP treatment.[9,10] Authors noted that modafinil could be started if there were no other identifiable causes for EDS, ruling out adherence or other issues with PAP (insufficient settings or fit), poor sleep hygiene, or other possible untreated or inadequately managed disorders that could contribute to EDS (depression, restless leg syndrome).[9] Currently, experts advise considering WPAs for persistent burdensome EDS symptoms (eg, with negative implications on quality of life, work productivity, or safety), excluding other causes, *and adjunctive to* adequate treatment for the underlying obstruction causing sleep apnea.[8] Stimulants such as amphetamines and methylphenidate are not recommended for routine use, not only since there is no supportive evidence for their use in OSA but also since they could pose cardiovascular risk (eg, hypertension, tachycardia) and addiction risk.

WPAs with approval for use in the OSA population include armodafinil, modafinil, and solriamfetol. Labeling for solriamfetol specifically recommends that this medication should be initiated after having

treated the underlying airway obstruction (eg, with continuous positive airway pressure [CPAP]) for at least one month and that the treatment modality for the underlying obstruction should be continued while on solriamfetol.[4]

Shift-Work Sleep Disorder (SWD)

An estimated 20% of US workers are employed in non-standard (ie, non-daytime) shift schedules with work performed regularly or intermittently (ie, rotating schedule) during the night or early morning.[7] While an adjustment in circadian rhythm may naturally occur for a fraction of people working nightshifts, others experience inadequate adjustment and suffer from shift-work sleep disorder (SWD).[40] SWD is characterized by sleep disturbances when sleep is intended and therefore impairments in alertness and cognitive performance occurring when the individual intends to be awake.[41] Sleep disturbances may include difficulty falling asleep or maintaining sleep, and poor sleep quality. Not only can SWD lead to serious occupational accidents and injury to one's-self or others, insufficient sleep can deteriorate social and emotional functioning, and has been associated with myocardial infarction, ischemic stroke, diabetes, and cancer in the shift-work population.[21,41-43]

The incidence of SWD is thought to occur between 5% to a third of shift workers.[21,41] This disorder is usually diagnosed based on sleep logs and actigraphy during work and work-free days, which involves a wearable watch-like device that measures activity levels. Actigraphy is also indicated to assess the response to therapy. To meet diagnosis criteria for SWD patients, must have chronic or recurrence of sleep-wake rhythm disruption due to shift work over at least 3 months with symptoms of excessive sleepiness **and/or** insomnia, reduced total sleep time, and associated with distress or impairment in mental, physical, social, occupational, or education functioning.[41,44]

Treatment

The following non-pharmaceutical approaches are recommended in the 2007 AASM guideline for the management of SWD: planned sleep schedules (Standard[†]), and timed light exposure (Guideline).[7] Regarding pharmacotherapies, modafinil is indicated to improve alertness during the nightshift for patients with SWD (Guideline). Other options include timed melatonin administration (Guideline), hypnotics to promote daytime sleep by relieving insomnia (Guideline; yet potential carryover effects into the work-shift should be weighed), and caffeine to improve alertness during the nightshift (Option).[7] This guideline did not consider armodafinil, also approved for SWD, which was introduced to the market later. Only armodafinil and modafinil have FDA indications for the treatment of shift-work sleep disorder. A more recent systematic review by Cochrane (2015) reported the following conclusions based on RCT evidence:[45]

- Low-quality evidence suggests that melatonin can lengthen daytime sleep duration following a nightshift (mean change in sleep time during the day was 24 minutes)
- Modafinil and armodafinil increase alertness and reduce sleepiness to some extent but are associated with headache and nausea

[†] Refer to the bottom of table 4 on page 14 for a description of the recommendation categories from AASM

- Moderate-quality evidence suggests that armodafinil may reduce sleepiness by about one point on the Karolinska Sleepiness Scale (based on 2 trials with 3 month follow-up) and increases alertness. Modafinil probably has similar effects as armodafinil on sleepiness (moderate quality evidence; 1 trial)

- A low-quality trial showed that the hypnotic, zopiclone, did not improve sleep length or quality after a night shift

Brief Overview of Off-Label Uses for WPAs

i. The 2007 AASM guideline recommended **modafinil** for the treatment of excessive daytime sleepiness in the following conditions[5] (refer to the bottom of Table 4 on page 14 for descriptions of the recommendation ratings provided in parentheses)
   - idiopathic hypersomnia, recurrent hypersomnia, and hypersomnia due to a medical condition (Option),
   - Parkinson's disease (Option),
   - myotonic dystrophy (Option),
   - multiple sclerosis (Guideline)
   - hypersomnias of central origin (Option)

ii. Other off-label uses for **modafinil** with some supportive evidence, in addition to being recommended in clinical guidelines include the following, as described in Lexicomp:[46]
   - Severe cancer-related fatigue in patients receiving active treatment (level of evidence [LOE]: B, G)[‡]
   - Augmentation to antidepressant treatment for major depressive disorder (LOE: C, G)
   - Multiple sclerosis–related fatigue (LOE: C, G)
   - Parkinson disease–related excessive daytime sleepiness (LOE: C, G)

   No off-label uses are described for armodafinil, solriamfetol, or pitolisant in Lexicomp. Micromedex lists bipolar depression as an off-label use, with positive outcomes demonstrated in RCT evidence; and no off-label uses for the newer agents.[47]

iii. Systematic reviews that we are aware of regarding studies for off-label uses, mainly with modafinil, include the following conditions: traumatic brain injury, diencephalic stroke or multiple sclerosis[48]; augmentation for acute depressive episodes in bipolar disorders[49]; negative symptoms of schizophrenia,[50] fatigue due to Parkinson's disease,[51] and idiopathic hypersomnia.[52]

[‡]Evidence ratings as assigned by Lexicomp: **B**, evidence from randomized, controlled trials with important limitations, or very strong evidence of some other research design; **C**, evidence from observational studies, unsystematic clinical experience, or randomized, controlled trials with major limitations, where the estimate of effect is more uncertain; **G,** use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Pharmacology

Armodafinil is an R-enantiomer of modafinil, a 1:1 mixture of R- and S-enantiomers.[1,2] The exact mechanism for stimulating wakefulness of these agents is not fully understood, but they are known to inhibit dopamine reuptake in the brain, increasing dopamine, but to a lesser degree compared to amphetamines—perhaps related to less GABA release with modafinil and/or the additional effect of amphetamines inhibiting monoamine oxidase breakdown of dopamine.[2,53-55] The lower dopaminergic activity of modafinil coincides with its reputation as having lower addiction potential compared to amphetamines or methylphenidate (DEA schedule IV versus schedule II products).[53] Animal-based studies suggest that modafinil has more localized neuronal activation on the wake-promoting areas of the brain vs. amphetamine.[53] Other proposed mechanisms of action of modafinil include increased release of glutamate and activation of the hypocretin system as shown in animal models.[53] The wakefulness-inducing effect of modafinil can be attenuated by the α1- adrenergic receptor antagonist, prazosin.[1]

The half-life of R-modafinil (ie, armodafinil) is about three times longer than S-modafinil in adults.[1] The concentration-time profiles of the R-enantiomer are similar with a single 50 mg dose of armodafinil compared to that from a 100 mg dose of modafinil.[2] When comparing similar milligram dosages, the steady-state exposure per Cmax and AUC with 200 mg armodafinil were approximately 37% and 70% higher, respectively, compared that with 200 mg of modafinil "… due to the more rapid clearance of the S-enantiomer [with modafinil] (elimination half-life approximately 4 hours) as compared to the R-enantiomer."[2]

Solriamfetol is thought to increase wakefulness by its action as a dopamine and norepinephrine reuptake inhibitor (DNRI), particularly in the brainstem arousal system, to promote wakefulness; however, the downstream actions that yield this effect are not completely clear.[56] Solriamfetol increases extracellular concentrations of these neurotransmitters, however, does not promote monoamine release as do traditional stimulants.[57] Although the agent increases norepinephrine, the pharmacologic effect does not seem to include modification of cataplexy.[55,58]

Pitolisant enhances wakefulness through activity as an antagonist/inverse agonist at histamine-3 (H3) receptors.[19,59] It has binding specificity for H3 receptors where it blocks the down-regulatory effect of histamine or other H3-receptor agonists ultimately enhancing histaminergic synthesis and release from tuberomammillary neurons in the brain—an area thought to control wakefulness and cognitive functions.[12,19] Histamine is thought to promote wakefulness through the cortical and subcortical neurons in concert with orexin and inhibits both non-REM and REM sleep-promoting neurons. Pitolisant's action also indirectly increases release of additional wake-promoting neurotransmitters such as acetylcholine, dopamine, and norepinephrine.[55,59] However, the location of enhanced dopamine activity does not appear to involve the areas of the brain strongly tied to dependence/addiction (ie, prefrontal cortex rather than the striatal complex of the nucleus accumbens).[55,59]

Table 5 provides pharmacokinetic information for these agents.

Table 5. Pharmacokinetic Information [1-4]

	Time to maximum concentration (Tmax) and Elimination half-life ($T_{1/2}$)	Metabolism Excretion	Other Notes
Armodafinil (Nuvigil)	**Tmax: 2 hours**; may be delayed by 2-4 hours if taken with food **$T_{1/2}$: 15 hours**	Amide hydrolysis and **CYP 3A4/5** metabolism Elimination information specific for R-enantiomer is not provided; see information on modafinil	Systemic exposure may be as much as 15% higher in elderly subjects (>65 years of age) vs. younger adults; consider use of lower doses in elderly
Modafinil (Provigil)	**Tmax: 2-4 hours**; may be delayed by 1 hour if taken with food **$T_{1/2}$** after multiple doses**: 15 hours**	Amide hydrolysis and **CYP 3A4/5** metabolism Mainly metabolized via liver; 81% of dose excreted, mainly as metabolites, through urine (<10% as parent compound); about 1.0% excreted via feces. Auto-induction of metabolism may occur however the consistency of this in adults and the whether it is clinical significant is unclear	Clearance of modafinil may be reduced in the elderly (by potentially 20%); consider use of lower dosages in elderly
Solriamfetol (Sunosi)	**Tmax: 2 hours**; may be delayed by 1 hour if taken with food **$T_{1/2}$: 7 hours**	Excreted primarily unchanged (95% of dose) as parent compound in urine, likely via active tubular secretion	Age (eg, >65) did not have considerable effect on PK
Pitolisant (Wakix)	**Tmax**: **3.5 hours** (2 to 5 hours); food did not have a significant effect **T $_{1/2}$**: **20 hours** (7.5 to 24.2 hours) following a single dose of 35.6mg	Primarily via **CYP2D6** (CYP3A4, minor) to inactive metabolites 90% excreted via urine with <2% unchanged drug; and 2.3% via feces	A PK study with 12 elderly subjects (age 68 to 82 years) did not show exposure differences compared to younger adults

Abbreviations: PK, pharmacokinetic; CYP, cytochrome P450; Tmax, time to maximum concentration; Tss, time to steady state

Direct Comparative Evidence

Systematic reviews describe 2 head-to-head studies in total, both with pitolisant versus modafinil for the treatment of narcolepsy.[11-17] Together, these studies suggest that pitolisant dosages on the high end of the approved range (17.8 mg to 35.6 mg per day[§]) reduce sleepiness (assessed by the Epworth Sleepiness Scale [ESS]) similarly to modafinil 100-400 mg per day; yet, pitolisant did not demonstrate non-inferiority to modafinil[18] and modafinil may outperform the lower dosage range of pitolisant (ie, 4.5 mg to 17.8 mg per day) for improvement in the ESS score. The ESS score is based on a self-administered questionnaire reflecting sleep liability during hypothetical daily activities, where lower scores reflect less symptom severity.[18] There were no significant differences found between pitolisant and modafinil for secondary endpoints related to wakefulness maintenance, attention level, ESS percent responders, and cataplexy rate in either study.[18]

No other direct comparison studies were identified for other indications or drug comparisons. Several SRs published within the last year searched for studies on efficacy and tolerability of solriamfetol for its approved indications but show a lack of head-to-head RCTs.[26-28] Additionally, there were no studies identified comparing armodafinil directly to modafinil for approved indications, a consistent finding among several SRs located (SRs per indication: SWSD[60], ES-OSA[29], narcolepsy[24,25]). We did not identify any more recent head-to-head evidence after a supplemental literature search.

Pitolisant (PIT) vs. Modafinil (MOD) for Narcolepsy

Two double-blind, 8-week, multicenter, placebo-controlled RCTs compared pitolisant, modafinil, and placebo for the treatment of narcolepsy in adults.[16,61,62] Patients were randomized to 1 of the 3 arms, with a flexible dosing regimen during the first 3 weeks, then a stable dosage for 5 weeks. Pitolisant dosing ranged from 10-40 mg/day in Harmony I and a lower range of 5-20 mg/day in Harmony 1- bis. Modafinil dosing range was 100-400 mg/day in each study. Patients were eligible if they were 18 years or older with symptoms consistent with narcolepsy with or without cataplexy, were free of psychostimulants for at least 14 days prior to screening, and had excessive daytime sleepiness defined as an ESS score of 14 or more at baseline. Patients were allowed to continue anti-cataplectic drugs (sodium oxybate or antidepressants). Most patients entering the studies had cataplexy at baseline: 81%, 82%, and 80% in the pitolisant, modafinil, and placebo arms in Harmony I, respectively. The primary endpoint for both studies was the difference in the change from baseline (CFB) of ESS scores between pitolisant and placebo groups at week 8.[63]

After 8 weeks of treatment, in Harmony I (N=95, NCT01067222), pitolisant performed similarly to modafinil but failed to demonstrate non-inferiority to modafinil (mean difference in CFB in ESS score was 0.12 95% CI −2.5, 2.7; p=0.250 for PIT vs. MOD). The confidence interval extended outside of the pre-specified non-inferiority margin of 2 points so did not demonstrate non-inferiority. Additionally, there were no statistical differences between pitolisant- and modafinil-treated groups at week 8 with

[§] 4.45 mg, 17.8 mg, and 35.6mg pitolisant free base are equivalent to 5 mg, 20 mg, and 40 mg pitolisant hydrochloride

respect to scores for maintaining wakefulness (per the maintenance of wakefulness test [MWT][**]), attention level (per sustained attention to response task [SART][††]), ESS responder rate (responder defined as achieving a final ESS of ≤10), or rates of cataplexy (ie, attacks per week).[18,64] Note that the trial was not specifically powered to detect differences in the cataplexy rate. Compared to placebo, pitolisant was superior for reducing ESS by about 3 points (mean difference of –3.0 95% CI –5.6, –0.4; p=0·024) and with respect to secondary endpoints showing improvement in MWT (by 1.4 minutes) or better ESS responder and cataplexy rates.[18,64]

Harmony 1-bis (N=166, NCT01638403) has not been fully published, but information from the European drug-approval review shows that modafinil outperformed pitolisant for reducing the ESS score (MOD *vs.* PIT treatment difference was -2.75 ESS points; p =0.002); though, pitolisant performed similarly to modafinil for maintaining wakefulness (per MWT) and cataplexy rate.[12,63] Pitolisant was superior to placebo for improvement in ESS (when clustering data),[65] ESS responder rate, and improvement in MWT score in Harmony 1-bis at week 8.[62] A smaller treatment effect observed in Harmony 1-bis, around 2 points difference from placebo (-2.2 95% CI -4.17, -0.22)[3]compared to that observed in Harmony I (difference from placebo of -3.0 95% CI -5.6, -0.4; p=0·024), may have been due to the lower dosage range studied in the 1-bis trial: 61% and 26% of patients reached a stable dose of **35.6 mg** and 17.8 mg, respectively, in Harmony 1; whereas, 63% and 24% of patients reached a stable maximum dose of **17.8mg** and 9.8 mg, respectively, in Harmony 1-bis.[63]

Safety

Discontinuation or intolerability to WPAs may be related to headache or nausea, which are 2 of the more common side effects with these medications, or possibly due to other less frequent side effects such as nervousness or anxiety, dry mouth, decreased appetite, insomnia, and GI symptoms (eg, diarrhea or constipation). Patients should be warned of rare but serious hypersensitivity reactions possible with armodafinil/modafinil.[1,2] WPAs as a class should be used cautiously in patients with psychiatric history and the dose should be reduced or discontinued if psychiatric symptoms develop or exacerbate. Although infrequent, hallucinations have been reported with the use of armodafinil, modafinil, and pitolisant, but potential contribution from sleep deprivation should also be considered with such symptom.[1-3] Since these agents can slightly increase blood pressure (BP) and/or heart rate (HR), particularly modafinil, armodafinil and solriamfetol,[1-4,19,20] patients with hypertensive history should have their blood pressure well-controlled before starting treatment and should be monitored for BP or HR excursions after stating treatment, following an increase in the dose, and periodically during treatment. Use of armodafinil/modafinil should be avoided in patients with history of left ventricular hypertrophy or with history of mitral valve prolapse during previous use with stimulants.[1,2] Product

[**] The MWT is an objective measure for maintenance of wakefulness, reflected by the number of minutes a person is able to stay awake under sleep-promoting conditions; higher values translate to a greater degree of wakefulness
[††] The SART score is also an objective measure for vigilance and attention where patients must distinguish a certain number, by pushing a button, as they are shown over 225 rounds of numbers. The SART assessment produces error scores for the patient's response (eg, the number of missed responses, and the number of incorrect responses)

labeling for these 2 agents note that transient ischemic T-wave changes on ECG occurred in 3 patients either with mitral valve prolapse or left ventricular hypertrophy during clinical studies.[2]

With the exception of pitolisant which is not a scheduled substance, these agents have risk of misuse and abuse (as schedule IV substances) since they can produce some psychoactive or euphoric effects[1,2] or drug-liking effects.[4] However, these agents seem to have a lower risk of abuse/addiction compared to the schedule II stimulants (eg, amphetamines and methylphenidate) possibly related to lower dopaminergic activity in the nucleus accumbens.[53] Prescription refill patterns for the controlled products can be reviewed and assessed for appropriateness by prescribers on the Utah Controlled Substance Database.

Table 6 provides a summary of the labeled warnings for these agents.

Table 6. Warnings and Precautions [1-4]

Armodafinil and Modafinil	Pitolisant	Solriamfetol
	CONTRAINDICATION	
Hypersensitivity to armodafinil or modafinil	Severe hepatic impairment; Hypersensitivity to pitolisant	Use within 14 days or concomitantly with a monoamine oxidase inhibitor
	QTc PROLONGATION	
SERIOUS HYPERSENSITIVITY REACTION Rare but serious hypersensitivity cases have been reported (eg, serious rash, Seven's Johnson Syndrome, Angioedema, and Anaphylaxis, drug reaction with eosinophilia and system symptoms [DRESS], and multi-organ hypersensitivity)	Avoid in patients with history of QT prolongation or other cardiac arrhythmias; if taking other QTc prolonging drugs; or who have symptomatic bradycardia, hypokalemia or hypomagnesemia (predisposing factors). Monitor QTc in patients with hepatic or renal impairment	
PERSISTENT SLEEPINESS Provide warning to patients that the medication may not completely normalize their level of wakefulness and if they remain sleepy, they should avoid driving or other potentially dangerous activity. Prescribers should directly question patients about residual drowsiness.		
PSYCHIATRIC SYMPTOMS Use with caution in patients with a history of psychosis, depression, or mania; use may be related to increased feelings of anxiety, agitation, nervousness, and irritability. Consider discontinuation if psychiatric symptoms develop		**PSYCHIATRIC SYMPTOMS** Use with caution in patients with history of psychosis or bipolar disorders. Consider dose reduction or discontinuation if psychiatric symptoms develop
KNOWN CARDIOVASCULAR DISEASE Consider increased monitoring of heart rate (HR) and blood pressure (BP); patients may require new or increased dosage of antihypertensive. These agents may slightly increase BP and HR		**BLOOD PRESSURE & HEART RATE** Measure heart rate and blood pressure prior to initiation and during treatment since the medication may increase slightly BP and HR

Table 6. Warnings and Precautions [1-4]

Armodafinil and Modafinil	Pitolisant	Solriamfetol
Recommended to avoid in patients with history of left ventricular hypertrophy or with mitral valve prolapse occurrence while previously receiving stimulants.		Ensure blood pressure is controlled prior to initiation; use with caution in patients with cardiovascular risk factors
MAY CAUSE FETAL HARM	**RISKS TO FETUS IS UNCLEAR**	
Potential fetal harm based on animal studies (modafinil with pregnancy category C)	There are not clear drug-associated risks based on human case reports. Animal studies showed embryofetal toxicity when used at supra-therapeutic doses (ie, exposures higher than expected with the maximum recommended dose). A pregnancy exposure registry is available for these agents and providers are encouraged to register pregnant patients.	

Abbreviations: BP, blood pressure; HR, heart rate

In the single comparative study with pitolisant and modafinil**,** there were no changes in cardiovascular parameters in either group.[18] Adverse events reported in ≥5% of patients in one arm vs. another were the following (percentage represents the proportion of patients in each arm experiencing the event)[18]:

- There were more patients experiencing the following event who were treated with modafinil vs. pitolisant: abdominal pain/discomfort (18% vs. 6%), diarrhea (12% vs. 3%), dizziness (12% vs. 3%), withdrawal symptoms (10% vs. 0%), and anxiety (6% vs. 0%).
- There were more patients experiencing the following event who were treated with pitolisant vs. modafinil: headache (35% vs. 18%), and insomnia (10% vs. 0%).

The 4 WPAs have potential drug interactions either related to CYP metabolism for armodafinil, modafinil, and pitolisant, or related to MAOI use for solriamfetol (see **Table 7**). Of these agents, pitolisant has potential to prolong the QTc interval so ideally should not be used with other drugs known to prolong QTc or in patients who have arrhythmia history or risk factors for QTc prolongation.

Table 7. Drug Interactions [1-4,66]

Armodafinil & modafinil

- May increase exposure to **CYP2C19 substrates** such as omeprazole, phenytoin, and diazepam
- **Steroidal contraceptives** (e.g., ethinyl estradiol); must use an alternative or add on method of contraception while taking modafinil or armodafinil and for 1 month after their discontinuation
- Cyclosporine exposure may be reduced

Pitolisant

- Use up to a maximum dose of 17.9 mg once daily while taking a strong **CYP2D6 inhibitor**
- May consider a dose increase during use with strong **CYP3A4 inducers**
- Pitolisant may decrease exposure to sensitive **CYP3A4 substrates** such as hormonal contraceptives; use an alternative non-hormonal contraceptive during treatment with pitolisant and at least 21 days following pitolisant discontinuation
- Avoid use with **drugs that also increase the QT interval** and in patients with risk factors for prolonged QT interval.

Table 7. Drug Interactions [1-4,66]

Solriamfetol

- Avoid use with **MAOIs** or within 14 days following MAOI treatment (contraindication) since this could cause a life-threatening hypertensive reaction.
- Use with caution while in combination with other drugs that may increase blood pressure and/or heart rate; or with dopaminergic drugs or norepinephrine reuptake inhibitors since such combined used has not been assessed.

Common adverse events (AEs) as reported in package inserts

- Armodafinil: occurring in ≥5% of patients were headache, nausea, dizziness, and insomnia.
- Modafinil: occurring in ≥5% of patients were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia
- Pitolisant: occurring in ≥5% of patients and at least twice that of placebo were insomnia (6%), nausea (6%), and anxiety (5%)
- Solriamfetol: occurring in ≥ 5% of patients and greater than placebo were headache, nausea, decreased appetite, insomnia, and anxiety

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Appendix A: Literature Searches

Table 1. Search Strategy for **Ovid MEDLINE(R)** and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 24, 2021

#	Searches	Results
1	Modafinil/ or Wakefulness-Promoting Agents/ or *Wakefulness/de [Drug Effects]	2102
2	dopamine uptake inhibitors/ or Central Nervous System Stimulants/ or Histamine H3 Antagonists/ or "Drug Inverse Agonism"/	27160
3	(armodafinil or Nuvigil or modafinil or Provigil or solriamfetol or SUVN-G3031 or Sunosi or pitolisant or Wakix or (dopamine adj5 inhibitor*) or stimulant* or (wake* adj promot*)).ti,ab,kw,kf.	32533
4	1 or 2 or 3	53759
5	Sleep Apnea, Obstructive/ or Narcolepsy/ or "Disorders of Excessive Somnolence"/ or Cataplexy/ or Narcolepsy/ or Sleep Disorders, Circadian Rhythm/	29827
6	(narcolep* or cataple* or gelineau* or hypersomn* or shift-work* or (excessive adj2 (sleepiness or somnolence)) or wakeful*).ti,ab,kw,kf.	27436
7	5 or 6	50549
8	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	396189
9	(Medline or Embase or Pubmed or search).tw. or (systematic-review or meta-analysis).tw,pt.	599929
10	8 or 9	651783
11	4 and 7 and 10	106 Potential SRs
12	(armodafinil or Nuvigil or modafinil or Provigil or solriamfetol or SUVN-G3031 or Sunosi or pitolisant or Wakix).ti,ab,kw,kf. or Modafinil/	2082
13	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1259693
14	7 and 12 and 13	317
15	limit 14 to yr="2013 -Current"	119 Potential RCTs
16	11 or 15	198

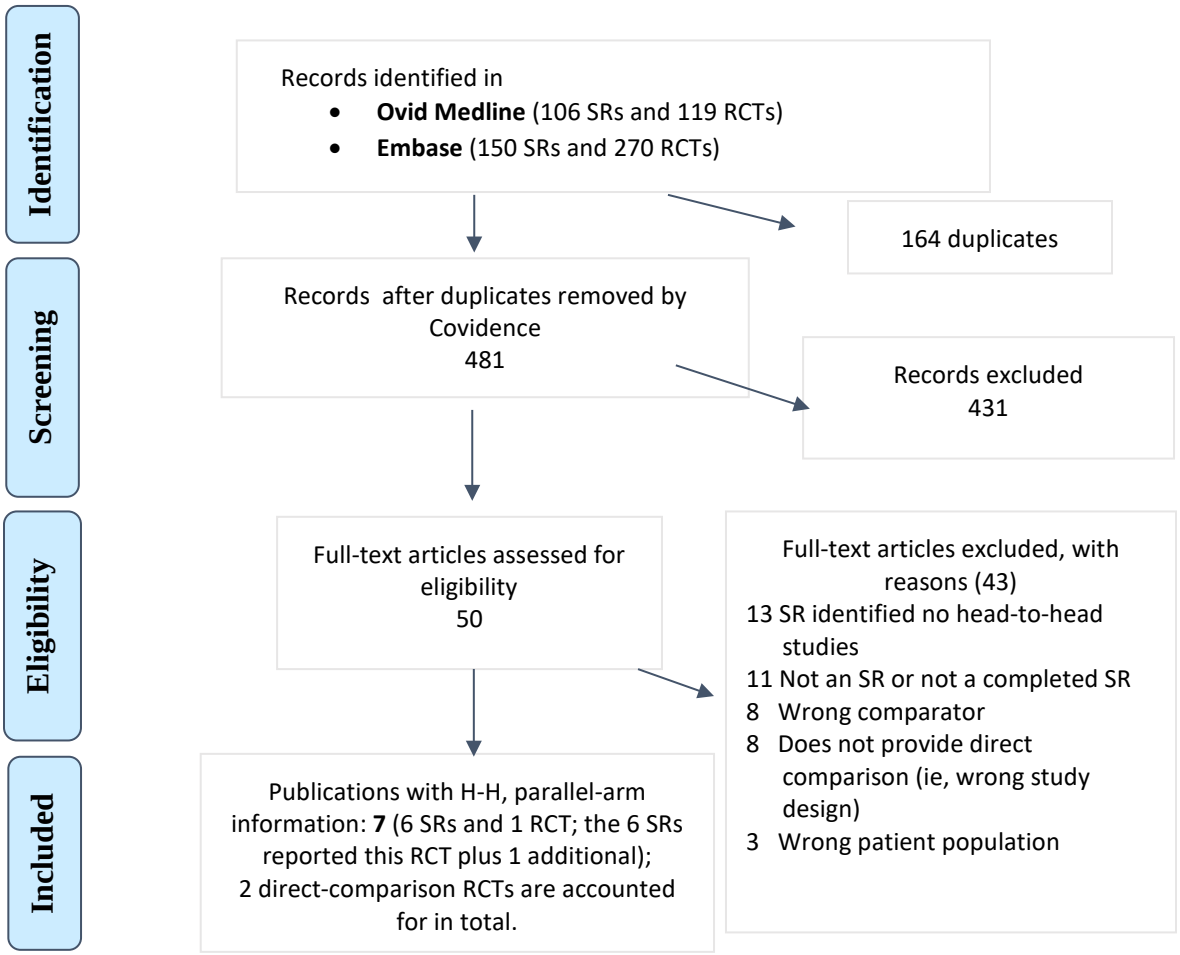
Table 2. Embase Searched on May 24th

	Results
	Potential SRs and RCTs (Unique) **393**
#19 **#8** OR **#18**	
	Total RCTs **270**
#18 **#14** OR **#17**	
	RCTs for SWD, extra 3 years **31**
#17 **#6** AND **#9** AND **#15** AND [2013-2021]/py	
	88
#16 **#6** AND **#9** AND **#15**	
	7,992
#15 '**shift work disorder**'/exp OR '**shift work***':ti,ab,kw	
	RCTs from 2016 onward **249**
#14 **#7** AND **#9** AND **#12** AND [2016-2021]/py	
	645
#13 **#7** AND **#9** AND **#12**	
	6,581
#12 **#10** OR **#11**	
	6,387
#11 '**modafinil**'/exp OR '**armodafinil**'/exp OR '**solriamfetol**'/exp OR '**pitolisant**'/exp	
	3,066
#10 **armodafinil**:ti,ab,kw OR **nuvigil**:ti,ab,kw OR **modafinil**:ti,ab,kw OR **provigil**:ti,ab,kw OR **solriamfetol**:ti,ab,kw OR '**suvn g3031**':ti,ab,kw OR **sunosi**:ti,ab,kw OR **pitolisant**:ti,ab,kw OR **wakix**:ti,ab,kw	
	1,415,708
#9 ('**clinical study**'/mj OR '**clinical trial**'/mj OR '**controlled clinical trial**'/mj OR '**major clinical study**'/mj OR '**randomized controlled trial**'/exp OR '**randomized controlled trial (topic)**'/exp OR '**control group**'/mj OR (((**clinical** OR **randomi*** OR **controlled** OR '**double-blind**') NEAR/3 (**study** OR **trial**)):ti,ab) OR **placebo**:ab,ti OR '**head to head**':ti,ab) AND [english]/lim	
	Potential SRs **150**
#8 **#5** AND **#6** AND **#7**	

	108,888
#7 #3 OR #4	**171,071**
#6 #1 OR #2	**419,482**
#5 (**cochrane***:jt OR '**systematic review***':jt OR '**meta analysis**'/exp OR '**systematic review**'/exp OR ((**systematic*** NEAR/3 **review***):ti,ab,kw) OR ((**systematic*** NEAR/2 **search***):ti,ab,kw) OR '**meta analys***':ti,ab,kw OR **metaanalys***:ti,ab,kw OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)) NOT ('**conference abstract**'/it OR '**conference review**'/it) AND [english]/lim	**41,922**
#4 **narcolep***:ti,ab,kw OR **cataple***:ti,ab,kw OR **gelineau***:ti,ab,kw OR **hypersomn***:ti,ab,kw OR '**shift work***':ti,ab,kw OR ((**excessive** NEXT/2 (**sleepiness** OR **somnolence**)):ti,ab,kw) OR **wakeful***:ti,ab,kw	**81,823**
#3 '**sleep disordered breathing**'/mj OR '**central sleep apnea syndrome**'/mj OR '**narcolepsy**'/exp OR '**cataplexy**'/exp OR '**hypersomnia**'/exp OR '**shift work disorder**'/exp OR '**sleep disorder**'/mj	**40,681**
#2 **armodafinil**:ti,ab,kw OR **nuvigil**:ti,ab,kw OR **modafinil**:ti,ab,kw OR **provigil**:ti,ab,kw OR **solriamfetol**:ti,ab,kw OR '**suvn g3031**':ti,ab,kw OR **sunosi**:ti,ab,kw OR **pitolisant**:ti,ab,kw OR **wakix**:ti,ab,kw OR ((**dopamine** NEXT/5 **inhibitor***):ti,ab,kw) OR **stimulant***:ti,ab,kw	**148,362**
#1 '**wakefulness promoting agent**'/exp OR '**central stimulant agent**'/de OR '**modafinil**'/exp OR '**armodafinil**'/exp OR '**alpha 1 adrenergic receptor stimulating agent**'/de OR '**adrenergic receptor stimulating agent**'/de OR '**solriamfetol**'/exp OR '**pitolisant**'/exp OR '**histamine h3 receptor antagonist**'/exp OR '**dopamine uptake inhibitor**'/exp	

Appendix B: Screening of Studies

Figure 1. PRISMA Flow Chart for Publication Screening



Abbreviations: H-H, head to head; RCT, randomized controlled trial; SR, systematic review

Excluded Studies by Reason

No direct-comparison effect estimate provided for WPAs of interest (ie, wrong study design)

1. Bron M, Franek J, Ronnebaum S, Menno D, Bujanover S, Stepnowsky C. Indirect treatment comparison of the efficacy of solriamfetol, modafinil, and armodafinil for the treatment of excessive sleepiness in obstructive sleep apnea. *Journal of Managed Care and Specialty Pharmacy*. 2018;24(10 A):S56.
2. Bron M, Ronnebaum S, Kratochvil D, et al. Indirect treatment comparison of the efficacy and safety of solriamfetol, modafinil, and armodafinil for the treatment of excessive daytime sleepiness in obstructive sleep apnoea. *Sleep Medicine*. 2019;64((Bron M.; Menno D.; Bujanover S.) Jazz Pharmaceuticals, Palo Alto, CA, United States(Ronnebaum S.; Kratochvil D.; Patel D.) Pharmerit International LP, Bethesda, MD, United States(Stepnowsky C.) University of California San Diego, La Jolla, CA, United Sta):S51-S52.
3. Caussé C, Lehert P. Comparison of Modafinil and Pitolisant in narcolepsy: A non inferiority meta-analytical approach. *Journal of Sleep Research*. 2020;29(SUPPL 1).
4. Caussé C, Lehert P. Narcolepsy treatments: Comparison of pitolisant, modafinil and sodium oxybate via a network meta-analysis. *Journal of Sleep Research*. 2020;29(SUPPL 1).
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6. Lehert P, Falissard B. Multiple treatment comparison in narcolepsy: a network meta-analysis. *Sleep*. 2018;41(12)
7. Plazzi G, Lehert P. Narcolepsy treatments: Comparison of pitolisant, modafinil and sodium oxybate via a network meta-analysis. *Sleep Medicine*. 2017;40((Plazzi G.) Scienze Mediche - Neuromotorie, Universita Di Bologna, Bologna, Italy(Lehert P.) Faculty of Medicine, University of Melbourne, Melbourne, Australia):e263-e264.
8. Taneja A, Saharia P, Chadha N, Rajput A, Goel A. A network meta-analysis on comparative efficacy and safety of investigationa l and approved therapies for the treatment of narcolepsy. *Value in Health*. 2016;19(3):A60.

Not an SR or not a completed SR (ie, protocol only)

1. Abad VC, Guilleminault C. Solriamfetol for the treatment of daytime sleepiness in obstructive sleep apnea. *Expert review of respiratory medicine*. 2018;12(12):1007-1019.
2. Bogan RK. Armodafinil in the treatment of excessive sleepiness. *Expert opinion on pharmacotherapy*. 2010;11(6):993-1002.
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4. Baumann CR. Wide implications of a trial on pitolisant for cataplexy. *The Lancet Neurology*. 2017;16(3):173-174.
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6. Chang XC, Lu XX, Hong WK. Stimulant drugs for narcolepsy in adults. *Cochrane Database of Systematic Reviews*. 2015;2015(11).
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8. Fratoni AJ, Chamberlin KW. Sunosi for excessive sleepiness in adults with narcolepsy or obstructive sleep apnea. *Drug Topics*. 2020;164(1):23.
9. Gandhi KD, Mansukhani MP, Silber MH, Kolla BP. Excessive Daytime Sleepiness: A Clinical Review. *Mayo Clinic proceedings*. 2021;96(5):1288-1301.

10. Powell J, Piszczatoski C, Garland S. Solriamfetol for Excessive Sleepiness in Narcolepsy and Obstructive Sleep Apnea. *The Annals of pharmacotherapy*. 2020;54(10):1016-1020.
11. Snedecor SJ, Mayer G, Thorpy MJ, Dauvilliers Y. Multiple treatment comparison in narcolepsy: A network meta-analysis-methodological concerns. *Sleep*. 2019;42(5).

Inclusion criteria open to head-to-head studies but the authors did not identify any head-to-head studies for WPAs of interest

1. Avellar ABCC, Carvalho LBC, Prado GF, Prado LBF. Pharmacotherapy for residual excessive sleepiness and cognition in CPAP-treated patients with obstructive sleep apnea syndrome: A systematic review and meta-analysis. *Sleep medicine reviews*. 2016;30(9804678):97-107.
2. Ballon JS, Feifel D. A systematic review of modafinil: Potential clinical uses and mechanisms of action. *The Journal of clinical psychiatry*. 2006;67(4):554-566.
3. Brown JN, Wilson DT. Safety and efficacy of armodafinil in the treatment of excessive sleepiness. *Clinical Medicine Insights: Therapeutics*. 2011;3((Brown J.N., jamie.brown2@va.gov) Pharmacy Service, Durham VA Medical Center, Durham, NC 27705, United States(Wilson D.T.) Campbell University College of Pharmacy and Health Sciences, Buies Creek, NC 27506, United States):159-169.
4. Kumar R. Approved and investigational uses of modafinil : an evidence-based review. *Drugs*. 2008;68(13):1803-1839.
5. Kuan Y-C, Wu D, Huang K-W, et al. Effects of Modafinil and Armodafinil in Patients With Obstructive Sleep Apnea: A Meta-analysis of Randomized Controlled Trials. *Clinical therapeutics*. 2016;38(4):874-888.
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7. Liira J, Verbeek J, Ruotsalainen J. Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. *JAMA*. 2015;313(9):961-962.
8. Neil-Sztramko SE, Pahwa M, Demers PA, Gotay CC. Health-related interventions among night shift workers: a critical review of the literature. *Scandinavian journal of work, environment & health*. 2014;40(6):543-556.
9. Nishino S, Okuro M. Emerging treatments for narcolepsy and its related disorders. *Expert opinion on emerging drugs*. 2010;15(1):139-158.
10. Savarese M, Di Perri MC. Excessive sleepiness in shift work disorder: a narrative review of the last 5 years. *Sleep & breathing = Schlaf & Atmung*. 2020;24(1):297-310.
11. Subedi R, Singh R, Thakur RK, K C B, Jha D, Ray BK. Efficacy and safety of solriamfetol for excessive daytime sleepiness in narcolepsy and obstructive sleep apnea: a systematic review and meta-analysis of clinical trials. *Sleep medicine*. 2020;75(100898759):510-521.
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13. Wise MS, Arand DL, Auger RR, Brooks SN, Watson NF. Treatment of narcolepsy and other hypersomnias of central origin: An American Academy of Sleep Medicine review. *Sleep*. 2007;30(12):1712-1727.

Wrong Comparator

1. Bhat A, El Solh AA. Management of narcolepsy. *Expert opinion on pharmacotherapy*. 2008;9(10):1721-1733.
2. Chapman J, Vakulin A, Yee B, Marshall N. Modafinil and armodafinil in obstructive sleep apnoea. A systematic review and meta-analysis. *Sleep and Biological Rhythms*. 2014;12((Chapman J.; Vakulin A.; Yee B.; Marshall N.) NHMRC Centre of Research Excellence, NeuroSleep, Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia(Vakulin A.) Adelaide Institute for Sleep Health, Flinders University, Adelaide):13.

3. Chapman JL, Vakulin A, Yee BJ, Marshall NS. Modafinil and armodafinil in obstructive sleep apnoea. A systematic review and meta-analysis. *Journal of Sleep Research*. 2014;23((Chapman J.L.; Vakulin A.; Yee B.J.; Marshall N.S.) Sleep and Circadian Research Group, Woolcock Institute of Medical Research, Glebe, NSW, Australia(Chapman J.L.; Vakulin A.; Yee B.J.; Marshall N.S.) NHMRC Centre for Integrated Research and Understanding):199.
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5. Dauvilliers Y, Schwartz JC, Davis C, Dayno J. Efficacy and safety of pitolisant in patients with narcolepsy: a review of clinical trials. *Sleep Medicine*. 2019;64((Dauvilliers Y.) Neurology, CHU Gui-de-Chauliac, Montpellier, France(Schwartz J.-C.) Bioprojet Pharma, Paris, France(Davis C.; Dayno J.) Harmony Biosciences LLC, Plymouth Meeting, United States):S85-S86.
6. Dauvilliers Y, Schwartz JC, Davis C, Dayno J. Efficacy and safety of pitolisant in patients with narcolepsy: A review of clinical trials. *Neurology*. 2019;92(15). Supplement
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8. Sukhal S, Khalid M, Tulaimat A. Effect of Wakefulness-Promoting Agents on Sleepiness in Patients with Sleep Apnea Treated with CPAP: A Meta-Analysis. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2015;11(10):1179-1186.

Wrong Patient Population

1. Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas SM, Sharkey KM. Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced Sleep-Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-W. *Journal of Clinical Sleep Medicine*. 2015;11(10):1199-1236.
2. Annane D, Moore DH, Barnes PRJ, Miller RG. Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. *The Cochrane database of systematic reviews*. 2006(3):CD003218.
3. Gasior M, Freeman J, Zammit G, et al. Maintenance of wakefulness with lisdexamfetamine dimesylate, compared with placebo and armodafinil in healthy adult males undergoing acute sleep loss. *Journal of clinical psychopharmacology*. 2014;34(6):690-696.