Treatment of Central Disorders of Hypersomnolence:
An American Academy of Sleep Medicine Clinical Practice Guideline

Introduction: This guideline establishes clinical practice recommendations for the treatment of central disorders of hypersomnolence in adults and children.

Methods: The American Academy of Sleep Medicine (AASM) commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths of treatment based on a systematic review of the literature and an assessment of the evidence using the GRADE process. The task force provided a summary of the relevant literature and the quality of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations that support the recommendations. The AASM Board of Directors approved the final recommendations.

Recommendations: The following recommendations are intended as a guide for clinicians in choosing a specific treatment for central disorders of hypersomnolence in adults and children. Each recommendation statement is assigned a strength (“Strong” or “Conditional”). A “Strong” recommendation (i.e., “We recommend...”) is one that clinicians should follow under most circumstances. A “Conditional” recommendation (i.e. “We suggest...”) is one that requires that the clinician use clinical knowledge and experience, and strongly considers the individual patient's values and preferences to determine the best course of action.

Adult patients with narcolepsy
1. We recommend that clinicians use modafinil for the treatment of narcolepsy in adults. (Strong)
2. We recommend that clinicians use pitolisant for the treatment of narcolepsy in adults. (Strong)
3. We recommend that clinicians use sodium oxybate for the treatment of narcolepsy in adults. (Strong)
4. We recommend that clinicians use solriamfetol for the treatment of narcolepsy in adults. (Strong)
5. We suggest that clinicians use armodafinil for the treatment of narcolepsy in adults. (Conditional)
6. We suggest that clinicians use dexmethylphenidate for the treatment of narcolepsy in adults. (Conditional)
7. We suggest that clinicians use methylphenidate for the treatment of narcolepsy in adults. (Conditional)
8. We suggest that clinicians not use clomipramine for the treatment of narcolepsy in adults. (Conditional)

Adult patients with idiopathic hypersomnia
9. We recommend that clinicians use modafinil for the treatment of idiopathic hypersomnia in adults. (Strong)
10. We suggest that clinicians use clarithromycin for the treatment of idiopathic hypersomnia in adults. (Conditional)
11. We suggest that clinicians use methylphenidate for the treatment of idiopathic hypersomnia in adults. (Conditional)
12. We suggest that clinicians use pitolisant for the treatment of idiopathic hypersomnia in adults. (Conditional)
13. We suggest that clinicians use sodium oxybate for the treatment of idiopathic hypersomnia in adults. (Conditional)

Adult patients with Kleine-Levin Syndrome
14. We suggest that clinicians use lithium for the treatment of Kleine-Levin syndrome in adults. (Conditional)

Adult patients with hypersomnia due to medical conditions and associated with psychiatric disorders

Hypersomnia secondary to alpha-synucleinopathies
15. We suggest that clinicians use armodafinil for the treatment of hypersomnia secondary to dementia with Lewy bodies in adults. (Conditional)
16. We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to Parkinson disease in adults. (Conditional)
17. We suggest that clinicians use sodium oxybate for the treatment of hypersomnia secondary to Parkinson disease in adults. (Conditional)

Posttraumatic hypersomnia
18. We suggest that clinicians use armodafinil for the treatment of hypersomnia secondary to traumatic brain injury in adults. (Conditional)
19. We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to traumatic brain injury in adults. (Conditional)
Adult patients with genetic disorders associated with primary central nervous system somnolence

20. We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to myotonic dystrophy in adults. (Conditional)

Pediatric patients with narcolepsy

21. We suggest that clinicians use modafinil for the treatment of narcolepsy in pediatric patients. (Conditional)
22. We suggest that clinicians use sodium oxybate for the treatment of narcolepsy in pediatric patients. (Conditional)

INTRODUCTION

This clinical practice guideline updates the previously published American Academy of Sleep Medicine (AASM) guidelines on the treatment of narcolepsy and other hypersomnias of central origin\(^1\) and reflects the current recommendations of the AASM.

This guideline, in conjunction with the accompanying systematic review,\(^2\) provides a comprehensive update of the available evidence and a synthesis of clinical practice recommendations for the treatment of narcolepsy and other hypersomnias of central origin. It is intended to optimize patient-centric care by broadly informing clinicians who care for adult and pediatric patients diagnosed with narcolepsy and other hypersomnias of central origin.

METHODS

The AASM commissioned a task force (TF) of sleep medicine clinicians with expertise in central disorders of hypersomnolence. The TF was required to disclose all potential conflicts of interest (COI), per the AASM’s COI policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM’s conflicts of interest policy, individuals were not allowed to be appointed to the TF if they reported a Level 1 COI professional or financial conflict that might diminish the integrity, credibility, or ethical standards of the guideline. Individuals reporting professional or financial conflicts that represented potential bias but did not prohibit participation in the development of the guideline, were required to recuse themselves from discussion or writing responsibilities related to the conflicts. All relevant conflicts of interest are listed in the Disclosures section.

The TF conducted a systematic review of the published scientific literature of United States Food and Drug Administration (FDA) approved prescription medications and non-pharmacologic interventions used clinically to treat central disorders of hypersomnolence, focusing on patient-oriented, clinically relevant outcomes. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material of the accompanying systematic review. The purpose of the review was to compare interventions for central nervous system hypersomnias and other hypersomnias of secondary origin to placebo, to determine whether the interventions provided clinically significant improvements in relevant outcomes. The clinical practice recommendations were then developed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process.\(^3,4\) The TF determined the direction and strength of each recommendation statement ("Strong" or "Conditional") based on the clinical significance of the critical outcomes and an overall assessment of the following GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use. Details of these assessments can be found in the accompanying systematic review. Additional information is provided in the form of “Remarks” immediately following the recommendation statements, when deemed necessary by the TF. Remarks are based on the evidence evaluated during the systematic review and are intended to provide context for the recommendations and to guide clinicians in the implementation of the recommendations in daily practice.

The recommendations in this guideline define principles of practice that should meet the needs of most patients in most situations. A “Strong” recommendation is one that clinicians should follow for almost all patients (i.e., something that might qualify as a Quality Measure). A “Conditional” recommendation reflects a lower degree of
certainty in the appropriateness of the patient-care strategy for all patients. It requires that the clinician use clinical knowledge and experience, and strongly considers the individual patient’s values and preferences to determine the best course of action. The ultimate judgment regarding any specific treatment must be made by the treating clinician and the patient, taking into consideration the individual circumstances of the patient, available treatment options, and resources. The AASM expects this guideline to have an impact on professional behavior, patient outcomes, and—possibly—health care costs. This clinical practice guideline reflects the state of knowledge at the time of publication and will be updated in the future as further research becomes available.

RECOMMENDATIONS

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the GRADE process. The recommendations reflect only those interventions for which there was sufficient evidence to make a recommendation. Interventions for which literature was reviewed but it was determined insufficient evidence existed to make a recommendation are discussed in the systematic review. The implications of the strength of recommendations for guideline users are summarized in Table 1. Remarks are provided to guide clinicians in the implementation of these recommendations.

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*The ultimate judgment regarding the suitability of any specific recommendation must be made by the clinician and their patient.*

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*Accident Risk and Work/School Performance/Attendance were Critical outcomes; however, no data were available.
RECOMMENDATIONS FOR ADULT POPULATIONS

The following are recommendations for the treatment of adults with central disorders of hypersomnolence namely, narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnias secondary to medical disorders.

Narcolepsy

Recommendations for specific interventions for the treatment of narcolepsy in adults are presented below. There was insufficient and inconclusive evidence to make recommendations for L-carnitine, naps, selegiline, triazolam selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). A summary of the evidence for each intervention can be found in the accompanying systematic review.

Recommendation 1: We recommend that clinicians use modafinil for the treatment of narcolepsy in adults. (STRONG)

Remark: This medication is a Federal Drug Administration (FDA) Schedule IV federally controlled substance because of its potential for abuse or dependency. A 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.

The TF assessed whether modafinil was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified nine RCTs and four observational studies assessing efficacy of modafinil in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness, cataplexy, disease severity and quality of life.

The overall quality of evidence was moderate. The quality of evidence was downgraded due to imprecision. Across all studies reporting the use of modafinil (irrespective of the indication), commonly reported adverse events included insomnia, nausea, diarrhea, headache and dry mouth. Based on their clinical expertise, the TF determined that the benefits of modafinil use in non-pregnant patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of modafinil. While costs of the medication are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their narcolepsy.

Recommendation 2: We recommend that clinicians use pitolisant for the treatment of narcolepsy in adults. (STRONG)

Remark: The drug is contraindicated in patients with severe hepatic impairment. It is not recommended in patients with end stage kidney disease and patients with cardiac arrythmias. Studies in animals have shown reproductive toxicity, including teratogenicity.

The TF assessed whether pitolisant was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified three RCTs evaluating pitolisant efficacy in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness and cataplexy.

The overall quality of evidence was high. Across all studies reporting the use of pitolisant (irrespective of the indication), commonly reported adverse events included headache, insomnia, weight gain and nausea. None of them resulted in treatment cessation.

Based on their clinical expertise, the TF determined that the benefits of pitolisant use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of pitolisant. This drug is only available through specialty pharmacies. While costs of the medication are likely to vary, the majority of patients would most likely use pitolisant compared to no treatment for their narcolepsy.

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Recommendation 3: We recommend that clinicians use sodium oxybate for the treatment of narcolepsy in adults. (STRONG)

Remark: This medication has an FDA black box warning stating that it is a central nervous system depressant and may cause respiratory depression. It is an FDA Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with seizures, respiratory depression, decreased consciousness, coma, and death especially if used in combination with other CNS depressants, such as alcohol.

The TF assessed whether sodium oxybate was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified six RCTs and six observational studies for the treatment of narcolepsy with sodium oxybate in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness, cataplexy, disease severity and quality of life.

The overall quality of evidence for sodium oxybate to treat narcolepsy compared to placebo was considered moderate. The quality of evidence was downgraded due to imprecision. Across all RCTs reporting on the use of sodium oxybate (irrespective of the indication), commonly reported adverse events included the occurrence of a variety of sleep disturbances including obstructive sleep apnea, nausea, dizziness, urinary/renal disturbances, headache and chest discomfort. Common adverse events in the observational studies included sleep disturbances, headache, nausea, dizziness and confusion.

Based on their clinical expertise, the TF determined that the benefits of sodium oxybate use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of sodium oxybate. This drug is only available through risk evaluation mitigation strategy (REMS) program using certified pharmacies. While costs of the medication are likely to vary, the majority of patients would most likely use sodium oxybate compared to no treatment for their narcolepsy.

Recommendation 4: We recommend that clinicians use solriamfetol for the treatment of narcolepsy in adults. (STRONG)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency.

The TF assessed whether solriamfetol was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified three RCTs assessing clinical efficacy of solriamfetol in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness and disease severity.

The overall quality of evidence for solriamfetol for the treatment of narcolepsy was considered high. Across all studies reporting the use of solriamfetol (irrespective of the indication), commonly reported adverse events included headache, decreased appetite, insomnia, nausea and chest discomfort. Most were moderate in severity.

Based on their clinical expertise, the TF determined that the benefits of solriamfetol use in patients outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of solriamfetol. While costs of the medication are likely to vary, the majority of patients would most likely use solriamfetol compared to no treatment for their narcolepsy.

Recommendation 5: We suggest that clinicians use armodafinil for the treatment of narcolepsy in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. While armodafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 5
The TF assessed whether armodafinil was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified one randomized controlled trial and one open label study with armodafinil in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness and disease severity.

The overall quality of evidence was moderate. The quality of evidence was downgraded due to imprecision. Across all studies reporting the use of armodafinil (irrespective of the indication), commonly reported adverse events included headache, upper respiratory tract infections, dizziness, nausea, sinusitis, and somnolence.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of armodafinil when used in non-pregnant patients. While costs of the medication are likely to vary, the majority of patients would probably use armodafinil compared to no treatment for their narcolepsy.

**Recommendation 6: We suggest that clinicians use dextroamphetamine for the treatment of narcolepsy in adults. (CONDITIONAL)**

*Remark: This medication is an FDA Schedule II federally controlled substance with a black box warning stating that it has a high potential for abuse and prolonged administration may lead to dependence.*

The TF assessed whether dextroamphetamine was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified one double blind randomized controlled trial, one single blind randomized controlled trial (RCT) and a retrospective observational long-term self-reported case series assessing efficacy of dexamphetamine in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness and cataplexy.

The overall quality of evidence was very low. The quality of evidence was downgraded due to imprecision. The most common side effects included sweatiness, a ‘living on the edge feeling’, weight gain, loss of appetite and irritability.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of dextroamphetamine. While costs of the medication are likely to vary, the majority of patients would probably use dexamphetamine compared to no treatment for their narcolepsy.

**Recommendation 7: We suggest that clinicians use methylphenidate for the treatment of narcolepsy in adults. (CONDITIONAL)**

*Remark: This medication is an FDA Schedule II federally controlled substance and has a black box warning stating that it should be given cautiously to patients with a history of drug dependence or alcoholism.*

The TF assessed whether methylphenidate was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified one observational prospective cohort study and one case series assessing the efficacy of methylphenidate in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in disease severity.

The overall quality of evidence was very low. The quality of evidence was downgraded due to imprecision. Across all studies reporting the use of methylphenidate (irrespective of the indication), the most common side effects were attributed to long-term drug treatment. These included dry mouth, sweating, headache, loss of appetite and stomach discomfort.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of methylphenidate. While costs of the medication are likely to vary, the majority of patients would probably use methylphenidate compared to no treatment for their narcolepsy.
**Recommendation 8:** We suggest that clinicians *not* use clomipramine for the treatment of narcolepsy in adults. (CONDITIONAL)

*Remark:* This drug has a FDA black box warning for suicidality for people under 24 years of age with psychiatric disorders.

The TF assessed whether clomipramine was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified one retrospective observational long-term, self-reported study for the treatment of narcolepsy with clomipramine in patients with narcolepsy type 1 and narcolepsy type 2. The study demonstrated a clinically significant improvement in excessive daytime sleepiness. The study utilized an unvalidated assessment tool of cataplexy and thus efficacy of clomipramine on cataplexy was not included in TF assessment.

The overall quality of evidence was very low. The quality of evidence was downgraded due to imprecision. Commonly reported adverse events included dry mouth, constipation, impaired sexual potency and delayed ejaculation. Costs of the medication are likely to vary.

Based on their clinical expertise, the TF concluded that the balance between the desirable and undesirable effects probably did not favor the use of clomipramine and that the majority of patients would probably not use this medication.

### Idiopathic Hypersomnia

Recommendations for specific interventions for the treatment of idiopathic hypersomnia (IH) in adults are presented below. There was insufficient and inconclusive evidence to make recommendations for flumazenil. A summary of the evidence for each intervention can be found in the accompanying systematic review.

**Recommendation 9:** We recommend that clinicians use modafinil for the treatment of idiopathic hypersomnia in adults. (STRONG)

*Remark:* This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. A 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.\(^5\)

The TF assessed whether modafinil was an effective treatment of idiopathic hypersomnia in adults based on improvements in excessive daytime sleepiness, disease severity, quality of life and work/school performance/attendance. The TF identified one RCT and four observational studies for the treatment of patients with idiopathic hypersomnia with modafinil. Three of these studies were retrospective, based on chart review. The studies demonstrated clinically significant improvements in excessive daytime sleepiness and disease severity.

The overall quality of evidence was moderate based on the RCT data for critical outcomes. The quality of evidence was downgraded due to imprecision. Across all studies reporting the use of modafinil (irrespective of the indication), commonly reported adverse events included insomnia, nausea, diarrhea, headache and dry mouth.

Based on their clinical expertise, the TF determined that the benefits of modafinil use in patients with idiopathic hypersomnia outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of modafinil. While costs of the medication are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their idiopathic hypersomnia.

**Recommendation 10:** We suggest that clinicians use clarithromycin for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)

*Remark:* This medication has an FDA alert on advising caution when using it in individuals with heart disease, because of the potential for increased risk of cardiac events and death in people with a history of myocardial infarction or angina. Additionally, because clarithromycin is an antibiotic, risks associated with antibiotic use (e.g.,

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antibiotic resistance, superinfection) should be weighed when considering the use of clarithromycin for patients with idiopathic hypersomnia.

The TF assessed whether clarithromycin was effective for the treatment of patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life and work/school performance/attendance. The TF identified one randomized controlled study and one observational retrospective study for the treatment of idiopathic hypersomnia with clarithromycin. These studies demonstrated clinically significant improvements in excessive daytime sleepiness, disease severity and quality of life.

The overall quality of evidence was moderate. The quality of evidence was downgraded due to imprecision. Commonly reported adverse events included gastrointestinal symptoms, dysgeusia or dysosmia, nausea, insomnia and diarrhea.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects on critical outcomes is likely in favor of clarithromycin. While costs of the medication are likely to vary, the majority of patients would probably use clarithromycin compared to no treatment for their idiopathic hypersomnia.

**Recommendation 11:** We suggest that clinicians use methylphenidate for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)

*Remark: This medication is an FDA Schedule II federally controlled substance and has a black box warning and stating that it should be given cautiously to patients with a history of drug dependence or alcoholism.*

The TF assessed whether methylphenidate was effective treatment of patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life and work/school performance/attendance. The TF identified one retrospective observational study for the treatment of idiopathic hypersomnia with methylphenidate. The study demonstrated a clinically significant improvement in disease severity.

The overall quality of evidence was very low, downgraded due to imprecision. Across all studies reporting the use of methylphenidate (irrespective of the indication), the most common side effects were attributed to long-term drug treatment. These included dry mouth, sweating, headache, loss of appetite and stomach discomfort.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of methylphenidate. While costs of the medication are likely to vary, the majority of patients would probably use methylphenidate compared to no treatment for their idiopathic hypersomnia.

**Recommendation 12.** We suggest that clinicians use pitolisant for the treatment of idiopathic hypersomnia. (CONDITIONAL)

*Remark: The drug is contraindicated in patients with severe hepatic impairment. It is not recommended in patients with end stage kidney disease and patients with cardiac arrhythmias. Studies in animals have shown reproductive toxicity, including teratogenicity.*

The TF assessed whether pitolisant was effective treatment of patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life and work/school performance/attendance. The TF identified one retrospective, observational study of pitolisant for idiopathic hypersomnia. The study demonstrated clinically significant improvement in excessive daytime sleepiness.

The overall quality of evidence was very low, based on the critical outcome reported in a single observational study. The quality of evidence was downgraded due to imprecision. Across all studies reporting the use of pitolisant (irrespective of the indication), commonly reported adverse events included headache, insomnia, weight gain and nausea. None of them resulted in treatment cessation.

Based on their clinical expertise, the TF determined that the benefits of pitolisant use in patients with idiopathic hypersomnia outweighed the risks of adverse events and that the balance between the desirable and undesirable effects probably favors the use of pitolisant. This drug is only available through specialty pharmacies. While costs
of the medication are likely to vary, the majority of patients would most likely use pitolisant compared to no treatment for their idiopathic hypersomnia.

**Recommendation 13. We suggest that clinicians use sodium oxybate for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)**

*Remark: This medication has an FDA black box warning stating that it is a central nervous system depressant and may cause respiratory depression. It is an FDA Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with seizures, respiratory depression, decreased consciousness, coma, and death especially if used in combination with other CNS depressants, such as alcohol.*

The TF assessed whether sodium oxybate was an effective treatment of patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life and work/school performance/attendance. The TF identified one retrospective, observational study that demonstrated a clinically significant improvement in excessive daytime sleepiness.

The overall quality of evidence was very low. The quality of evidence was downgraded due to imprecision. Across all RCTs reporting on the use of sodium oxybate (irrespective of the indication), commonly reported adverse events included the occurrence of a variety of sleep disturbances, nausea, dizziness, urinary/renal disturbances, headache and chest discomfort. Common adverse events in the observational studies included sleep disturbances, headache, nausea, dizziness and confusion.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate. It is only available through risk evaluation mitigation strategy (REMS) programs using certified pharmacies. While costs of the medication are likely to vary, the majority of patients would most likely use sodium oxybate compared to no treatment for their idiopathic hypersomnia.

**Kleine-Levin Syndrome**

Recommendations for specific interventions for the treatment of Kleine-Levin syndrome in adults are presented below. There was insufficient and inconclusive evidence to make recommendations for intravenous methylprednisolone. A summary of the evidence for each intervention can be found in the accompanying systematic review.

**Recommendation 14: We suggest that clinicians use lithium for the treatment of Kleine-Levin syndrome in adults. (CONDITIONAL)**

*Remark: This medication has a black box warning stating that lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy.*

The TF assessed whether lithium was an effective treatment of patients with Kleine-Levin Syndrome (KLS) based on improvements in disease severity, quality of life and work/school performance/attendance. The TF identified one prospective, open label, single center study that demonstrated a clinically significant improvement in disease severity.

The overall quality of evidence was very low. Quality of evidence was downgraded due to imprecision. There were no serious adverse events reported in the open label study of lithium among patients with KLS, with most common side effects being tremor, polyuria-polydipsia, diarrhea, and subclinical hypothyroidism. There was no report of lithium toxicity in this study.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of lithium for patients with KLS. Regular monitoring of the patient’s clinical state and of serum lithium concentrations is necessary. Serum concentrations should be determined twice per week during the acute phase, and until the serum concentrations and clinical condition of the patient have been stabilized. While costs of
the medication are likely to vary, the majority of patients would most likely use lithium compared to no treatment for their KLS.

**Hypersomnia secondary to medical conditions or associated with psychiatric conditions**

Recommendations for specific interventions for the treatment of pathophysiological subtypes of hypersomnia secondary to medical conditions or associated with psychiatric conditions in adults are presented below. There was insufficient and inconclusive evidence to make recommendations for modafinil for the treatment of hypersomnia secondary to brain tumors, infections, or other central nervous system lesions, and for liraglutide for the treatment of hypersomnia secondary to endocrine disorder.

**Hypersomnia secondary to alpha-synucleinopathies**

Recommendations for specific interventions for the treatment of hypersomnia secondary to alpha-synucleinopathies in adults are presented below. It is based on the clinical and pathophysiological subtypes identified in ICSD-3. There was insufficient and inconclusive evidence to make recommendations for light therapy. A summary of the evidence for each intervention can be found in the accompanying systematic review.

**Recommendation 15: We suggest that clinicians use armodafinil for the treatment of hypersomnia secondary to dementia with Lewy Bodies in adults. (CONDITIONAL)**

*Remark: This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. While armodafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.*

The TF assessed whether armodafinil was effective treatment of hypersomnia secondary to dementia with Lewy Bodies (DLB) in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. The TF identified one single arm, open label pilot study of armodafinil that demonstrated a clinically significant improvement in excessive daytime sleepiness in use in patients with DLB.

The overall quality of evidence for armodafinil for the treatment of hypersomnia due to DLB was very low. The quality of evidence was downgraded because of imprecision. Across all studies reporting the use of armodafinil (irrespective of the indication), commonly reported adverse events included headache, upper respiratory tract infections, dizziness, nausea, sinusitis, and somnolence.

Based on their clinical expertise, the TF concluded that the balance between the desirable and undesirable effects is likely in favor of armodafinil for the treatment of hypersomnia secondary to DLB. While costs of the medication are likely to be higher, the majority of patients would probably use armodafinil compared to no treatment for their hypersomnia secondary to dementia with Lewy Bodies.

**Recommendation 16: We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to Parkinson disease. (CONDITIONAL)**

*Remark: This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. An 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.*

The TF assessed whether modafinil was effective treatment of hypersomnia secondary Parkinson disease in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. The TF identified four RCTs and one observational study assessing the effect of modafinil in adult patients with hypersomnia secondary to Parkinson disease. These studies demonstrated a clinically significant improvement in excessive daytime sleepiness.
The TF concluded that the overall quality of data on modafinil for patients with Parkinson disease was moderate. The level of evidence was downgraded for imprecision. Across all studies reporting the use of modafinil (irrespective of the indication), commonly reported adverse events included insomnia, nausea, diarrhea, headache and dry mouth.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects across all disorders is in favor of modafinil. While costs of the medication are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their hypersomnia.

**Recommendation 17:** We suggest that clinicians use sodium oxybate for the treatment of hypersomnia secondary to Parkinson disease. (CONDITIONAL)

*Remark: This medication has a FDA black box warning stating that it is a central nervous system depressant and may cause respiratory depression. It is an FDA Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with seizures, respiratory depression, decreased consciousness, coma, and death especially if used in combination with other CNS depressants, such as alcohol.*

The TF assessed whether sodium oxybate was effective treatment of hypersomnia secondary to Parkinson disease in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. The TF identified one RCT and one observational study assessing the effect of sodium oxybate in adult patients with hypersomnia secondary to Parkinson disease. The study demonstrated a clinically significant improvement in excessive daytime sleepiness.

The overall quality of evidence for sodium oxybate for the treatment of hypersomnia secondary to Parkinson disease was moderate. The quality of evidence was downgraded because of imprecision. Across all RCTs reporting on the use of sodium oxybate (irrespective of the indication), commonly reported adverse events included the occurrence of a variety of sleep disturbances, nausea, dizziness, urinary/renal disturbances, headache and chest discomfort. Common adverse events in the observational studies included sleep disturbances, headache, nausea, dizziness and confusion.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate for patients with Parkinson disease. This drug is only available through risk evaluation mitigation strategy (REMS) programs using certified pharmacies. While costs of the medication are likely to vary, the majority of patients would most likely use sodium oxybate compared to no treatment for their hypersomnia.

**Posttraumatic hypersomnia**

Recommendations for specific interventions for the treatment of hypersomnia secondary to posttraumatic hypersomnia are presented below. A summary of the evidence for each intervention can be found in the accompanying systematic review.

**Recommendation 18:** We suggest that clinicians use armodafinil for the treatment of hypersomnia secondary to traumatic brain injury in adults. (CONDITIONAL)

*Remark: This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. An 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.*

The TF assessed whether armodafinil was effective treatment of post traumatic hypersomnia in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. The TF identified 1 RCT of armodafinil that demonstrated a clinically significant improvement in excessive daytime sleepiness in traumatic brain injury (TBI) patients.
The overall quality of evidence for armodafinil for the treatment of hypersomnia due to TBI was moderate. The quality of evidence was downgraded because of imprecision. Across all studies reporting the use of armodafinil (irrespective of the indication), commonly reported adverse events included headache, upper respiratory tract infections, dizziness, nausea, sinusitis, and somnolence.

Based on their clinical expertise, The TF concluded that the balance between the desirable and undesirable effects is likely in favor of armodafinil for the treatment of hypersomnia secondary to TBI. While costs are likely to be higher, the majority of patients would probably use armodafinil compared to no treatment for their narcolepsy.

**Recommendation 19:** We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to traumatic brain injury in adults. (CONDITIONAL)

*Remark: This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. An 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.*

The TF assessed whether modafinil was effective treatment of post traumatic hypersomnia in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. One RCT which examined the effect of modafinil on patients with hypersomnia secondary to traumatic brain injury (TBI) was identified. The study demonstrated a clinically significant improvement in excessive daytime sleepiness.

The TF concluded that the overall quality of data on modafinil for patients with TBI was moderate. The level of evidence was downgraded for imprecision. Across all studies reporting the use of modafinil, commonly reported adverse events included insomnia, nausea, diarrhea, headache and dry mouth.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects in patients with hypersomnia secondary to TBI is in favor of modafinil. While costs are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their hypersomnia.

**Genetic disorders associated with primary central nervous system somnolence**

Recommendations for specific interventions for the treatment of genetic disorders associated with primary central nervous system somnolence in adults are presented below. There was insufficient and inconclusive evidence to make recommendations for methylphenidate and selegiline. A summary of the evidence for each intervention can be found in the accompanying systematic review.

**Recommendation 20:** We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to myotonic dystrophy in adults. (CONDITIONAL)

*Remark: This medication is a FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. An 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.*

The TF assessed whether modafinil was effective treatment of hypersomnia secondary to myotonic dystrophy in adults based on improvements in excessive daytime sleepiness, quality of life and work/school performance/attendance. The TF identified two RCTs which examined the effect of modafinil on patients with myotonic dystrophy. These studies demonstrated clinically significant improvements in excessive daytime sleepiness.

The TF concluded that the overall quality of data on modafinil for patients with myotonic dystrophy was moderate. The level of evidence in each of the cases was downgraded for imprecision. Across all studies reporting the use of modafinil (irrespective of the indication), commonly reported adverse events included insomnia, nausea, diarrhea, headache and dry mouth.
Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects in patients with hypersomnia secondary to myotonic dystrophy is in favor of modafinil. While costs are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their hypersomnia.

RECOMMENDATIONS FOR PEDIATRIC POPULATIONS

The following are recommendations for the treatment of pediatric populations with narcolepsy. No recommendations are provided for the treatment of pediatric patients with idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia secondary to medical disorders and hypersomnia associated with psychiatric disorders due to insufficient evidence.

Narcolepsy

Evidence-based recommendations for various interventions in the treatment of narcolepsy in pediatric populations are presented below. There was insufficient and inconclusive evidence to make recommendations for intravenous immune globulin; however, a summary of evidence in published literature can be found in the accompanying systematic review.

Recommendation 21: We suggest that clinicians use modafinil for the treatment of narcolepsy in pediatric patients. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. The drug is not FDA approved for patients <17 years based on a black box warning for Stevens-Johnson syndrome (SJS) and psychosis based on case reports in pediatric patients. An 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.  

The TF assessed whether modafinil was effective for the treatment of narcolepsy in pediatric patients based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified two observational studies that examined the effect of modafinil in pediatric patients with narcolepsy. These studies demonstrated clinically significant improvements in disease severity and excessive daytime sleepiness.

The overall quality of evidence was very low. Evidence was downgraded due to imprecision. Adverse events included irritability, dry mouth, nausea and headaches. No severe reactions including SJS and psychosis were reported.

Based on their clinical expertise, the TF determined that the balance between the desirable and undesirable effects is likely in favor of modafinil for pediatric patients with narcolepsy. While costs are likely to vary, the majority of patients would most likely use modafinil compared to no treatment.

Recommendation 22: We suggest that clinicians use sodium oxybate for the treatment of narcolepsy in pediatric patients. (CONDITIONAL)

Remark: This medication has a FDA black box warning stating that it is a central nervous system depressant and may cause respiratory depression. It is an FDA Schedule III controlled substance and is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with seizures, respiratory depression, decreased consciousness, coma, and death especially if used in combination with other CNS depressants, such as alcohol.

The TF assessed whether sodium oxybate was effective for the treatment of narcolepsy in pediatric patients based on improvements in excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk and work/school performance/attendance. The TF identified one prospective double-blind, placebo-controlled, randomized-withdrawal, and open-label study and three observational studies that examined the effect of sodium
oxybate in pediatric patients with narcolepsy. These studies demonstrated clinically significant improvements in cataplexy, disease severity and excessive daytime sleepiness.

The overall quality of evidence for sodium oxybate to treat narcolepsy compared to placebo was considered moderate. The quality of evidence was downgraded due to imprecision. Common adverse events included weight loss, enuresis, nausea, vomiting, headache, decreased weight, decreased appetite, nasopharyngitis, and dizziness and rare but serious adverse effects included central sleep apnea, depression and suicidality.

Based on their clinical expertise, the TF determined that the benefits of sodium oxybate use in patients outweighed the risks and adverse events and that the majority of the patients with narcolepsy would likely use sodium oxybate compared to no treatment. It is only available through risk evaluation mitigation strategy (REMS) programs using certified pharmacies. While costs are likely to vary, the majority of patients would most likely use sodium oxybate compared to no treatment for their narcolepsy.

**DISCUSSION**

When treating patients with central disorders of hypsomnolence, clinicians should individualize treatment selections based on patients’ age, pregnancy status and reproductive planning, co-morbidities including cardiovascular disease, allergies/history of adverse events, risk of dependency/potential for drug misuse and goals of care. Some of the interventions recommended above are federally controlled substances or report animal studies demonstrating a potential risk during pregnancy or lactation. Some interventions also require close monitoring of the patient due to risks associated with the intervention. Thus, treatment choices may change over time with age and new life experiences/needs (e.g. changes in employment, family demands) and clinicians should regularly reassess treatment efficacy during follow-up visits. This guideline also includes newly FDA-approved narcolepsy treatments, namely solriamfetol and pitolisant for adults and sodium oxybate for pediatric populations. While this allows timely assessment for these treatments, information on post-marketing adverse effects are not available for such newer treatments limiting long term risk/benefit assessments. Clinicians should be aware that additional non-pharmacologic management with workplace or educational disability accommodations, sleep hygiene, naps and cognitive behavioral therapy/psychological support is often needed to optimally treat patients regardless of drug treatments used.

The TF developed these recommendations using GRADE, a state-of-the-art methodology for assessment of available evidence. This approach offers a rigorous, patient-centered, transparent system of evaluation. The TF rarely found existing studies that encompassed all critical and important outcomes delineated by patients and clinicians and were further challenged by small sample sizes in most studies reviewed. Furthermore, older or more established treatments infrequently were evaluated using a randomized control design in contrast to newer drugs and comparative effectiveness studies were virtually non-existent. Last, the TF relied on scant literature and mostly on expert opinion when defining outcome measures and clinical significance thresholds.

Despite these challenges, the TF developed evidence-based recommendations to provide clinicians with heightened confidence in prescribing currently available, FDA approved treatments. The TF was only able to make recommendations when sufficient data were present to guide decision-making and the full list of treatments evaluated can be found in the systematic review. The absence of inclusion of such interventions in this Clinical Practice Guideline should not be misinterpreted as a statement against their clinical use.
REFERENCES


