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SPECIAL ARTICLES

Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline

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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 commissioned a task force of experts in sleep medicine to develop recommendations and assign strengths to each recommendation, 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 to guide 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 (ie, "We recommend … ") is one that clinicians should follow under most circumstances. A "conditional" recommendation (ie, "We suggest … ") is one that requires that the clinician use clinical knowledge and experience and strongly consider the individual patient's values and preferences to determine the best course of action. Under each disorder, strong recommendations are listed in alphabetical order followed by the conditional recommendations in alphabetical order. The section on adult patients with hypersomnia because of medical conditions is categorized based on the clinical and pathological subtypes identified in ICSD-3. The interventions in all the recommendation statements were compared to no treatment.

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

Adult patients with idiopathic hypersomnia

8. We recommend that clinicians use modafinil for the treatment of idiopathic hypersomnia in adults. (STRONG)
9. We suggest that clinicians use clarithromycin for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)
10. We suggest that clinicians use methylphenidate for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)
11. We suggest that clinicians use pitolisant for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)
12. We suggest that clinicians use sodium oxybate for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)

Adult patients with Kleine-Levin syndrome

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

Adult patients with hypersomnia due to medical conditions

Hypersomnia secondary to alpha-synucleinopathies

14. We suggest that clinicians use armodafinil for the treatment of hypersomnia secondary to dementia with Lewy bodies in adults. (CONDITIONAL)
15. We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to Parkinson's disease in adults. (CONDITIONAL)
16. We suggest that clinicians use sodium oxybate for the treatment of hypersomnia secondary to Parkinson's disease in adults. (CONDITIONAL)

Posttraumatic hypersomnia

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

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

Adult patients with hypersomnia secondary to brain tumors, infections, or other central nervous system lesions

20. We suggest that clinicians use modafinil for the treatment of hypersomnia secondary to multiple sclerosis in adults. (CONDITIONAL)

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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)

Keywords: hypersomnia, narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome, dementia with lewy bodies, Parkinson's disease, traumatic brain injury, myotonic dystrophy, multiple sclerosis, treatment

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INTRODUCTION

This clinical practice guideline updates the previously published American Academy of Sleep Medicine (AASM) practice parameters 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. The order of the recommendations is not intended to convey prioritization but is listed from strong to conditional within each disorder group.

The following clinical practice recommendations are based on a systematic review and evaluation of evidence using the GRADE process.[3,4] The recommendations reflect only those interventions for which there was sufficient evidence to make a recommendation. The absence of inclusion of certain interventions in this clinical practice guideline should not be interpreted as a statement against their clinical use. Interventions for which literature was reviewed but it was determined that insufficient evidence existed to make recommendations are discussed in the systematic review.[2] "Insufficient evidence" to determine the effectiveness of a particular intervention does not mean that the intervention does not work, but that evidence is lacking to guide decision-making. Additional research is needed to determine the effectiveness of the intervention.

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, per the AASM's conflict of interest (COI) policy, prior to being appointed to the TF and throughout the research and writing of these documents. In accordance with the AASM's COI policy, individuals were not allowed to be appointed to the TF if they reported a level 1 COI or a 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 U.S. Food & Drug Administration (FDA)–approved prescription medications and nonpharmacologic interventions used clinically to treat central disorders of hypersomnolence, focusing on patient-oriented, clinically relevant outcomes. The scope of the literature review did not include data for the TF to make specific recommendations for pregnant and lactating women. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material of the accompanying systematic review.[2] The purpose of the review was to compare interventions for central nervous system hypersomnias and other hypersomnias of secondary origin to placebo and/or pre-/postintervention to determine whether the interventions provided clinically significant improvements in relevant outcomes. The clinical practice recommendations were then developed according to the GRADE process.[4,5] 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. There is no systematic way of obtaining detailed individual treatment costs in the United States, given variable payor systems, regional cost differences, and other factors. The TF also did not identify studies assessing the cost:benefit ratio for most medications; therefore, drug prices were de-emphasized in clinical guideline decisions because of the variability of costs to patients. Details of reviewed literature and GRADE assessments can be found in the accompanying systematic review.[2]

Drafts of the systematic review and accompanying guideline were made available for public comment for a 4-week period on the AASM website. AASM members, the general public, including patient advocacy groups and other relevant stakeholders were invited to provide feedback on the drafts. The TF took into consideration all the comments received and made decisions about whether to revise the draft based on the scope and feasibility of the comments. The final draft was then reviewed and approved by the AASM Board of Directors for publication.

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 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 (ie, 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

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Table 1—Implications of strong and conditional recommendations for users of AASM clinical practice guidelines.

Strong recommendation: "We recommend …"	Almost all patients should receive the recommended course of action. Adherence to this recommendation could be used as a quality criterion or performance indicator.
Conditional recommendation: "We suggest …"	Most patients should receive the suggested course of action; however, different choices may be appropriate for different patients. The clinician must help each patient determine if the suggested course of action is clinically appropriate and consistent with his or her values and preferences.

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

Table 2—Summary of recommended interventions in adult populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*			
		Excessive Daytime Sleepiness	Cataplexy	Disease Severity	Quality of Life
Narcolepsy					
Modafinil	Strong	✓		✓	✓
Pitolisant	Strong	✓	✓	✓	
Sodium Oxybate	Strong	✓	✓	✓	
Solriamfetol	Strong	✓		✓	✓
Armodafinil	Conditional	✓		✓	
Dextroamphetamine	Conditional	✓	✓		
Methylphenidate	Conditional			✓	
Idiopathic hypersomnia					
Modafinil	Strong	✓		✓	
Clarithromycin	Conditional	✓		✓	✓
Methylphenidate	Conditional			✓	
Pitolisant	Conditional	✓			
Sodium oxybate	Conditional	✓			
Kleine-Levin syndrome					
Lithium	Conditional			✓	
Hypersomnia secondary to medical conditions					
Hypersomnia secondary to alpha synucleinopathies					
Armodafinil	Conditional (for dementia with Lewy bodies)	✓			
Modafinil	Conditional (for Parkinson's disease)	✓			
Sodium oxybate	Conditional (for Parkinson's disease)	✓			
Posttraumatic hypersomnia					
Armodafinil	Conditional (for traumatic brain injury)	✓			
Modafinil	Conditional (for traumatic brain injury)	✓			
Genetic disorders associated with primary central nervous system somnolence					
Modafinil	Conditional (for myotonic dystrophy)	✓			
Hypersomnia secondary to brain tumors, infections, or other central nervous system lesions					
Modafinil	Conditional (for multiple sclerosis)	✓			

*Accident risk and work/school performance/attendance were critical outcomes; however, no data were available. ✓Critical outcomes showing clinically significant improvement.

patients. The implications of the strength of recommendations for guideline users are summarized in **Table 1**. **Table 2** summarizes the recommendations for interventions in adult population and **Table 3** for the pediatric population. The recommendations are made for a disease, not for a particular symptom. They require the clinician to use clinical knowledge and experience, and strongly

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Table 3—Summary of recommended interventions in pediatric populations.

Intervention	Strength of Recommendation	Critical Outcomes Showing Clinically Significant Improvement*			
		Excessive Daytime Sleepiness	Cataplexy	Disease Severity	Quality of Life
Narcolepsy					
Modafinil	Conditional	✓			
Sodium oxybate	Conditional	✓	✓	✓	

*Accident risk and work/school performance/attendance were critical outcomes; however, no data were available. ✓Critical outcomes showing clinically significant improvement.

consider the individual patient's values and preferences to determine the best course of action.

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. Remarks include FDA black box warnings, effect on pregnancy, oral contraceptive pill–related interactions, and any teratogenicity issues.

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.

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, and 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, scheduled naps, selegiline, triazolam selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). While narcolepsy exists in 2 forms, narcolepsy type 1 (NT1) and type 2 (NT2), many studies included participants with either form of narcolepsy (referred to "unspecified narcolepsy" in the systematic review); therefore, the task force chose to make combined recommendations for both narcolepsy types. A summary of the evidence for each intervention can be found in the accompanying systematic review.[2]

Recommendation 1: We recommend that clinicians use modafinil (vs no treatment) 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. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. Modafinil may reduce the effectiveness of oral contraception.[6]

The TF assessed whether modafinil was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 9 RCTs and 4 observational studies assessing the efficacy of modafinil in patients with narcolepsy type 1 and narcolepsy type 2. 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. 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 outweighed the risks and adverse events and that the balance between the desirable and undesirable effects is strongly in favor of modafinil. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 (vs no treatment) for the treatment of narcolepsy in adults. (STRONG)

Remark: Based on animal data, pitolisant may cause fetal harm. Human data are insufficient to determine risk. Pitolisant may reduce the effectiveness of oral contraception.

The TF assessed whether pitolisant was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 3 RCTs evaluating pitolisant efficacy in patients with narcolepsy type 1 and narcolepsy type 2. These studies demonstrated clinically significant improvements in excessive daytime sleepiness, cataplexy, and disease severity.

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The overall quality of evidence was moderate. 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 concluded that the majority of patients would most likely use pitolisant compared to no treatment for their narcolepsy. 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. This drug is only available through specialty pharmacies.

Recommendation 3: We recommend that clinicians use sodium oxybate (vs no treatment) 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 central nervous system depressants, such as alcohol and sedating medications. Based on animal data, sodium oxybate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether sodium oxybate was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 6 RCTs and 6 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, and disease severity.

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 nausea, dizziness, nocturnal enuresis, headache, chest discomfort, and sleep disturbances. Sleep-disordered breathing has also been reported. 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. This drug is only available through the risk evaluation mitigation strategy program using certified pharmacies. While the 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 (vs no treatment) 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. Based on animal data, solriamfetol may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether solriamfetol was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 3 RCTs assessing the 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 mild or 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 (vs no treatment) 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. Based on animal data, armodafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Armodafinil may reduce the effectiveness of oral contraception.*

The TF assessed whether armodafinil was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 1 randomized controlled trial and 1 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

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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 patients. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 (vs no treatment) 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. Based on animal data, dextroamphetamine may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether dextroamphetamine was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 1 double-blind RCT, 1 single-blind RCT, and 1 retrospective observational long-term self-reported case series assessing the efficacy of dextroamphetamine 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 adverse effects included sweatiness, edginess, 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the costs of the medication are likely to vary, the majority of patients would probably use dextroamphetamine compared to no treatment for their narcolepsy.

Recommendation 7: We suggest that clinicians use methylphenidate (vs no treatment) 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. Based on animal data, methylphenidate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether methylphenidate was effective for the treatment of narcolepsy in adults based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 1 observational prospective cohort study and 1 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 adverse 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the costs of the medication are likely to vary, the majority of patients would probably use methylphenidate compared to no treatment for their narcolepsy.

Idiopathic hypersomnia

Recommendations for specific interventions for the treatment of idiopathic hypersomnia 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.[2]

Recommendation 8: We recommend that clinicians use modafinil (vs no treatment) for the treatment of idiopathic hypersomnia in adults. (STRONG)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] Modafinil may reduce the effectiveness of oral contraception.

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 1 RCT and 4 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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.

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Recommendation 9: We suggest that clinicians use clarithromycin (vs no treatment) 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 (eg, antibiotic resistance, superinfection) should be weighed when considering the use of clarithromycin for patients with idiopathic hypersomnia. Based on animal data, clarithromycin may cause fetal harm. Labeling states that clarithromycin should not be used by pregnant women.

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 1 randomized controlled study and 1 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 10: We suggest that clinicians use methylphenidate (vs no treatment) 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 stating that it should be given cautiously to patients with a history of drug dependence or alcoholism. Based on animal data, methylphenidate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether methylphenidate was effective treatment for patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life, and work/school performance/attendance. The TF identified 1 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 adverse 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 11: We suggest that clinicians use pitolisant (vs no treatment) for the treatment of idiopathic hypersomnia in adults. (CONDITIONAL)

Remark: Based on animal data, pitolisant may cause fetal harm. Human data are insufficient to determine risk. Pitolisant may reduce the effectiveness of oral contraception.

The TF assessed whether pitolisant was effective treatment for patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease severity, quality of life, and work/school performance/attendance. The TF identified 1 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. This drug is only available through specialty pharmacies. While the 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 12: We suggest that clinicians use sodium oxybate (vs no treatment) 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 central nervous system depressants, such as alcohol and sedating medications. Based on animal data, sodium oxybate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether sodium oxybate was an effective treatment for patients with idiopathic hypersomnia based on improvements in excessive daytime sleepiness, disease

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severity, quality of life, and work/school performance/attendance. The TF identified 1 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. It is only available through risk evaluation mitigation strategy programs using certified pharmacies. While the 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.[2]

Recommendation 13: We suggest that clinicians use lithium (vs no treatment) 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. The accessibility of facilities to conduct prompt and accurate serum lithium determinations should be determined before initiating therapy. Based on animal studies, lithium may cause fetal harm. Human studies suggest fetal harm but are insufficient to determine risk.

The TF assessed whether lithium was effective treatment for patients with Kleine-Levin syndrome (KLS) based on improvements in disease severity, quality of life, and work/school performance/attendance. The TF identified 1 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 adverse 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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

Recommendations for specific interventions for the treatment of pathophysiological subtypes of hypersomnia secondary to medical conditions in adults as outlined in ICSD-3[7] are presented below. There was insufficient and inconclusive evidence to make recommendations for light therapy for hypersomnia secondary to alpha-synucleinopathies (Parkinson's disease), methylphenidate and selegiline for genetic disorders associated with primary central nervous system somnolence (myotonic dystrophy), and liraglutide for the treatment of hypersomnia secondary to endocrine disorders (diabetes mellitus).

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.[2]

Recommendation 14: We suggest that clinicians use armodafinil (vs no treatment) for the treatment of hypersomnia secondary to dementia with Lewy bodies in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, armodafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] Armodafinil may reduce the effectiveness of oral contraception.

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 1 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.

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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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 15: We suggest that clinicians use modafinil (vs no treatment) for the treatment of hypersomnia secondary to Parkinson's disease. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Modafinil may reduce the effectiveness of oral contraception.*

The TF assessed whether modafinil was effective treatment of hypersomnia secondary to Parkinson's disease in adults based on improvements in excessive daytime sleepiness, quality of life, and work/school performance/attendance. The TF identified 4 RCTs and 1 observational study assessing the effect of modafinil in adult patients with hypersomnia secondary to Parkinson's 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's 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 is in favor of modafinil for the treatment of hypersomnia secondary to Parkinson's disease. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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 16: We suggest that clinicians use sodium oxybate (vs no treatment) for the treatment of hypersomnia secondary to Parkinson's disease. (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 and sedating medications. Based on animal data, sodium oxybate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether sodium oxybate was effective treatment of hypersomnia secondary to Parkinson's disease in adults based on improvements in excessive daytime sleepiness, quality of life, and work/school performance/attendance. The TF identified 1 RCT and 1 observational study assessing the effect of sodium oxybate in adult patients with hypersomnia secondary to Parkinson's 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's 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's disease. This drug is only available through risk evaluation mitigation strategy (REMS) programs using certified pharmacies. While the 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.[2]

Recommendation 17: We suggest that clinicians use armodafinil (vs no treatment) for the treatment of hypersomnia secondary to traumatic brain injury in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, armodafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Armodafinil may reduce the effectiveness of oral contraception.*

The TF assessed whether armodafinil was effective treatment of posttraumatic 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

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excessive daytime sleepiness in patients with traumatic brain injury (TBI).

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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the costs are likely to be higher, the majority of patients would probably use armodafinil compared to no treatment for their narcolepsy.

Recommendation 18: We suggest that clinicians use modafinil (vs no treatment) for the treatment of hypersomnia secondary to traumatic brain injury in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Modafinil may reduce the effectiveness of oral contraception.*

The TF assessed whether modafinil was effective treatment of posttraumatic hypersomnia in adults based on improvements in excessive daytime sleepiness, quality of life, and work/school performance/attendance. One RCT that 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the 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.[2]

Recommendation 19: We suggest that clinicians use modafinil (vs no treatment) for the treatment of hypersomnia secondary to myotonic dystrophy in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Modafinil may reduce the effectiveness of oral contraception.*

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 2 RCTs that 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 RCTs 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. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the costs are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their hypersomnia.

Hypersomnia secondary to brain tumors, infections, or other central nervous system lesions

Recommendation 20: We suggest that clinicians use modafinil (vs no treatment) for the treatment of hypersomnia secondary to multiple sclerosis in adults. (CONDITIONAL)

Remark: This medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] *Modafinil may reduce the effectiveness of oral contraception.*

The TF assessed whether modafinil was effective treatment of hypersomnia secondary to multiple sclerosis in adults based on improvement in excessive daytime sleepiness. The TF

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identified 1 observational study that examined the effect of modafinil on patients with multiple sclerosis. 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 muscular sclerosis was very low. 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 in patients with hypersomnia secondary to multiple sclerosis is in favor of modafinil. The balance of risks and harms is likely different for pregnant and breastfeeding women. While the costs are likely to vary, the majority of patients would most likely use modafinil compared to no treatment for their hypersomnia.

Hypersomnia associated with a psychiatric disorder

There are no recommendations for specific interventions for the treatment of hypersomnia associated with a psychiatric disorder. Evidence obtained for modafinil and light therapy was insufficient and inconclusive. A summary of the evidence for each intervention can be found in the accompanying systematic review.[2]

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.[2] Review of the literature did not produce relevant data meeting inclusion criteria regarding treatments commonly used in pediatric narcolepsy such as methylphenidate, amphetamines, naps (scheduled), and SSRI/SNRI medications (for cataplexy).

Recommendation 21: We suggest that clinicians use modafinil (vs no treatment) 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 aged < 17 years based on a black box warning for Stevens-Johnson syndrome (SJS) and psychosis based on case reports in pediatric patients. Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk. A 2018 annual report of the ongoing armodafinil/modafinil pregnancy registry in the United States showed a higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.[6] Modafinil may reduce the effectiveness of oral contraception.

The TF assessed whether modafinil was effective for the treatment of narcolepsy in pediatric patients based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 1 observational study that examined the effect of modafinil in pediatric patients with narcolepsy. The study demonstrated clinically significant improvement in 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. The balance of risks and harms is likely different for pregnant and breastfeeding patients. While the 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 (vs no treatment) for the treatment of narcolepsy in pediatric patients. (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 and sedating medications. Based on animal data, sodium oxybate may cause fetal harm. Human data are insufficient to determine risk.

The TF assessed whether sodium oxybate was effective for the treatment of narcolepsy in pediatric patients based on improvements in excessive daytime sleepiness, cataplexy (when present), disease severity, quality of life, accident risk, and work/school performance/attendance. The TF identified 1 prospective double-blind, placebo-controlled, randomized-withdrawal, and open-label study and 3 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.

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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. The balance of risks and harms is likely different for pregnant and breastfeeding patients. It is only available through risk evaluation mitigation strategy (REMS) programs using certified pharmacies. While the 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 hypersomnolence, clinicians should individualize treatment selections based on patients' age, pregnancy status and reproductive planning, comorbidities 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 and/or report 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 (eg, 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 postmarketing adverse effects is not available for such newer treatments, limiting long-term risk/benefit assessments. Clinicians should be aware that additional nonpharmacologic management with workplace or educational disability accommodations, sleep hygiene, and cognitive-behavioral therapy/psychological support is often needed to optimally treat patients regardless of drug treatments used. The scope of the literature review did not include data for the TF to make specific recommendations for pregnant and lactating women.

The TF developed these recommendations using GRADE, a state-of-the-art methodology for assessment of available evidence.[4,5] 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. Treatment costs to patients vary in the United States and cost:benefit data were unavailable to guide TF decision-making. Furthermore, older or more established treatments were rarely evaluated using a randomized controlled trial design in contrast to newer drugs and comparative effectiveness studies were virtually nonexistent. Last, the TF relied on scant literature and mostly on expert opinion when defining outcome measures and clinical significance thresholds.

The TF evaluated the data in support of individual medications, rather than for entire medication classes. However, medications used for the hypersomnia disorders often have enantiomers, racemic compounds, or prodrugs that might also be used for treatment (eg, modafinil and armodafinil, or dextroamphetamine, amphetamine salts, and lisdexamfetamine). Although we did not make class-wide medication recommendations, it may be reasonable to assume that closely related compounds will have similar risks and benefits.

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.[2] The absence of inclusion of such interventions in this clinical practice guideline should not be misinterpreted as a statement against their clinical use.

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DISCLOSURE STATEMENT

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