https://doi.org/10.5664/jcsm.9326

JCSM | Journal of Clinical Sleep Medicine

REVIEW ARTICLES

Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment

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Introduction: This systematic review provides supporting evidence for the accompanying clinical practice guideline on the treatment of central disorders of hypersomnolence in adults and children. The review focuses on prescription medications with U.S. Food & Drug Administration approval and nonpharmacologic interventions studied for the treatment of symptoms caused by central disorders of hypersomnolence.

Methods: The American Academy of Sleep Medicine commissioned a task force of experts in sleep medicine to perform a systematic review. Randomized controlled trials and observational studies addressing pharmacological and nonpharmacological interventions for central disorders of hypersomnolence were identified. Statistical analyses were performed to determine the clinical significance of all outcomes. Finally, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to assess the evidence for the purpose of making specific treatment recommendations.

Results: The literature search identified 678 studies; 144 met the inclusion criteria and 108 provided data suitable for statistical analyses. Evidence for the following interventions is presented: armodafinil, clarithromycin, clomipramine, dextroamphetamine, flumazenil, intravenous immune globulin (IVIG), light therapy, lithium, L-carnitine, liraglutide, methylphenidate, methylprednisolone, modafinil, naps, pitolisant, selegiline, sodium oxybate, solriamfetol, and triazolam. The task force provided a detailed summary of the evidence along with the quality of evidence, the balance of benefits and harms, patient values and preferences, and resource use considerations.

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

Citation: Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med.* 2021;17(9):1895–1945.

INTRODUCTION

This systematic review provides a detailed background on the treatment of central disorders of hypersomnolence, a discussion of the evidence identified in the review and all statistical analyses performed, and a discussion of the GRADE-related decisions that were made for the purposes of making clinical practice recommendations, which can be found in the accompanying guideline.[1] As classified in the *International Classification of Sleep Disorders,* third edition (ICSD-3),[2] excessive sleepiness of central origin includes both primary and secondary hypersomnias. The specific disorders included in this systematic review are narcolepsy type 1 (NT1, narcolepsy with cataplexy) and type 2 (NT2, narcolepsy without cataplexy), idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia associated with medical conditions, and hypersomnia associated with psychiatric disorders.

The aims of the present analysis are (1) to assess the efficacy of individual U.S. Food & Drug Administration (FDA)–approved prescription medications and nonpharmacologic interventions for the treatment of hypersomnia, (2) to evaluate the potential for adverse effects of these interventions, and (3) to identify gaps in the treatment research literature and offer recommendations for optimizing quality and uniformity of future investigations.

BACKGROUND

The first milestone in pharmacotherapy for central disorders of hypersomnolence occurred in 1956 with the publication of preliminary results on the treatment of methylphenidate for sleepiness associated with narcolepsy.[3] Subsequent advances in sleep medicine, including the publication of the *International Classification of Sleep Disorders*[2,4,5] as well as the worldwide growth of professional sleep societies, have resulted in the recognition of numerous primary disorders of sleepiness.

Central disorders of hypersomnolence are characterized by a complaint of hypersomnia not attributable to another sleep disorder disturbing nocturnal sleep (eg, obstructive sleep apnea), insufficient sleep, and/or circadian dysrhythmias. The presence of hypersomnolence disorders due to central origin denotes an inability to remain awake/alert during the major wakefulness episodes of the day, resulting in daily periods of irrepressible

need to sleep or daytime elapses into sleep.[2] Diagnostic criteria of all CNS disorders of hypersomnolence mandate that the complaint be present for at least 3 months, except for Kleine-Levin syndrome, which requires recurrent episodes, and hypersomnia due to a medication or substance, for which there is no minimum symptom duration. Diagnostic criteria can be found in the *International Classification of Sleep Disorders*, third edition (ICSD) and characteristic symptoms are reviewed below.

NT1 is characterized by the presence of cataplexy and the defined pathophysiology of orexin neuronal loss. The etiology of orexin cell destruction is not known although an autoimmune-mediated phenomenon is suspected. NT2 is characterized by an absence of cataplexy or absence of low orexin if measured. The underlying pathophysiology of NT2 is unknown and present data suggest a heterogeneous disorder. The most common and bothersome symptom of narcolepsy is excessive daytime sleepiness. However, disrupted nighttime sleep (defined by frequent waking periods during the night) also commonly occurs in narcolepsy, especially NT1. The functional impact of cataplexy varies between patients with NT1 depending on frequency, subtypes (partial vs full), social impact, and potential for injury/falls. While core narcolepsy symptoms include sleep paralysis and hypnagogic/hypnopompic hallucinations, patients typically report that their daily functions are more impaired by general symptoms of fatigue and cognitive difficulties.[6,7] Clinical presentations may differ among childhood patients as daytime sleepiness may manifest as hyperactivity, inattention, and emotional dysregulation.

In contrast to narcolepsy, patients with idiopathic hypersomnia typically report nonrestorative sleep (despite high sleep efficiency on nocturnal polysomnography), prolonged and severe sleep inertia, long sleep durations, and impaired daytime cognitive functions on a near-daily basis.

Patients with Kleine-Levin syndrome have recurrent bouts of hypersomnia (minimum of 2) that persist for 2 days or longer. During an episode of sleepiness, those afflicted exhibit marked behavioral changes including disinhibition, perceptual abnormalities, cognitive dysfunction, and eating disorders. No such symptoms are apparent during intervening periods of normal alertness. Although the pathophysiology of Kleine-Levin syndrome is unknown, functional imaging and electroencephalographic findings support thalamic, temporal, and frontal lobe involvement.[8,9]

If pathologic sleepiness is determined to be a direct result of an underlying medical or neurological condition, then a diagnosis of hypersomnia due to a medical disorder is invoked. This sleep disorder may be related to conditions such as neurodegenerative diseases, traumatic brain injury, cancers, and autoimmune conditions. Psychiatric conditions may also be *associated* with hypersomnia, and diagnostic criteria reflect a wholly clinical assessment. Multiple sleep latency test results among this latter group of patients are typically normal, but extended time in bed is frequently reported.

Common to all central disorders of hypersomnolence, impairments in alertness predispose individuals to serious decrements in performance and function. Consequently, patients' symptoms can significantly impact quality of life and personal safety, and create myriad additional adverse consequences for the afflicted, their social circle, and society at large. Proper treatment is therefore of paramount importance, and the AASM has been at the forefront of developing practice guidelines, including those pertaining to the primary hypersomnias.[10–12]

The initial 1994 consensus-based practice parameters for the treatment of narcolepsy described efficacy in the treatment of sleepiness with conventional stimulants such as amphetamines, methylphenidate, and pemoline, in presumed descending order of potency.[12] When these directives were updated in 2001,[11] evidence-based guidelines were based on growing clinical trial data and reporting of adverse events (adapted from Sackett[13]). The practice parameters favored the recently introduced modafinil, based upon a relative abundance of rigorously designed industry-sponsored studies. Other treatments such as selegiline and pemoline with lower-quality evidence and serious adverse effects were given lesser endorsement. Notably, specific endorsement of methylphenidate for pediatric populations was provided, based upon its widespread use in attention-deficit disorders (ADD), in contrast to the broader endorsement of various stimulants in the 1994 publication.[12] The 2001 practice guideline also highlighted possible treatments for another important symptom of narcolepsy, ie, cataplexy, with specific mention of tricyclic antidepressants and fluoxetine.[11]

A similar evidence-based assessment was utilized[14] in the 2007 practice parameters.[10,15] During the time that elapsed from the prior publication, additional studies emerged supporting the use of modafinil and sodium oxybate—the first FDA-approved treatment for cataplexy, daytime sleepiness, and disrupted sleep related to narcolepsy. Ritanserin was also newly introduced as a potential therapy for narcolepsy-associated sleepiness. Continued use of traditional stimulants was endorsed, with acknowledgment that limited published data reflected scarce sources of research funding for medications available in generic form. The aforementioned selegiline recommendation was further downgraded based upon limited clinical experience and potential medication and/or diet-induced reactions, and the pemoline recommendation was removed, in accordance with its removal from the market. Additional anticataplectic agents were described in the form of venlafaxine, reboxetine, and selective serotonin reuptake inhibitors generally, rather than fluoxetine specifically.

The emergence of several studies also allowed for consideration of treatments for other disorders of sleepiness in the 2007 practice parameters, with specific mention of modafinil as a potential agent for idiopathic hypersomnia and for daytime sleepiness due to Parkinson's disease, multiple sclerosis, and myotonic dystrophy. Methylphenidate was also listed as an option for sleepiness associated with the latter condition, based upon a small single study. Lithium carbonate was suggested as a treatment for Kleine-Levin syndrome (hypersomnia and behavioral symptoms), based upon a small case series and group consensus. The recommendation for use of methylphenidate for pediatric disorders of hypersomnolence remained unchanged, and modafinil was additionally recommended based upon 1 publication.[10]

The present document serves as the most recent AASM systematic review regarding the treatment of central disorders of hypersomnolence. Perhaps the biggest change in comparison to previous versions is the use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system of evidence analysis.[16] The TF considered the following domains of GRADE: quality of evidence, benefits and harms,

patient values and preferences, and resources use. In addition to being more rigorous in many respects than the previously employed evidence assessments, the GRADE process is also designed to result in more clinically relevant systematic reviews by requiring a combined consideration of strength of evidence with assessment of bias, risk/benefit analyses, and determination of patient values and preferences. As such, in the accompanying guideline,[1] many previously recommended interventions such as SSRIs/SNRIs for cataplexy associated with NT1 or traditional stimulants for idiopathic hypersomnia may be left inconclusive using GRADE, leaving some questions unanswered. While this certainly points out significant gaps in current clinical research pertaining to central disorders of hypersomnolence, the updated recommendations are intended to provide clinicians with heightened confidence in prescribing reviewed treatments and serve as a roadmap for future clinical trials needed to fill knowledge gaps.

METHODOLOGY

Expert task force

The AASM commissioned a task force (TF) comprising of board-certified sleep medicine specialists who are experts in the treatment of 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, TF members with a level 1 conflict were not allowed to participate. TF members with a level 2 conflict were required to recuse themselves from any related discussion or writing responsibilities. All relevant conflicts of interest are listed in the Disclosures Statement.

PICO questions

Patient population, intervention, comparison, and outcomes (PICO) questions were developed by the TF based on a review of the existing AASM practice parameters on the treatment of central disorders of hypersomnolence and an examination of systematic reviews, guidelines, and clinical trials published for adult and pediatric populations. The AASM Board of Directors (BOD) approved the final list of PICO questions, presented in **Table 1,** before the literature search was performed.

In addition, the TF developed a list of patient-oriented, clinically relevant outcomes to determine whether the various interventions, compared to no treatment, should be recommended for clinical practice. Input from stakeholders (patients, caregivers, and health care providers) was also taken into consideration. The TF rated the relative importance of each outcome to determine which outcomes were critical for decision-making. A summary of these "critical" outcomes by PICO is presented in **Table 2.** The TF specified other clinical outcomes such as fatigue, difficulty waking up in the morning, cognitive performance, sleep inertia, mood, and sleep quality as important but not critical for the clinical management of the hypersomnias.

Based on expert opinion and literature review, the TF set a clinical significance threshold (CST) for tools of interest for each outcome to determine whether the mean changes in the outcomes assessed were clinically significant. The CST was defined as the minimum level of improvement in the outcome of interest that would be considered clinically important to clinicians and patients. A summary of the CSTs for the clinical outcome measures is presented in **Table 3.** Where no clearly established threshold values could be determined, CSTs were determined based on consensus in conjunction with the TF literature review of commonly used thresholds for the various tools, gathering input from other sleep specialists, clinical judgment, and experience.

Literature searches, evidence review, and data extraction

The TF performed an extensive review of the scientific literature to retrieve articles that addressed the PICO questions. Separate literature searches were performed by the AASM research staff for each PICO question using PubMed, Embase, and International Pharmaceutical Abstracts (IPA; **Figure 1**). Articles that met inclusion criteria but did not report outcomes of interest were rejected from the final evidence base. The key terms, search limits, and inclusion/exclusion criteria specified by the TF are detailed in the supplemental material. Randomized controlled trials (RCTs) and observational studies that were cited in the prior AASM practice parameters were included for data analysis only if they met the current inclusion criteria.

The initial search of PubMed and Embase using the systematic review methods filter was undertaken in February 2017. A second literature search was performed in August 2017. A third literature search was performed in October 2018 to identify studies that were published since the second literature search to update the body of evidence for the review. The final literature search was conducted in August 2020. This last search did not yield any new publications. The TF reviewed previously published guidelines, systematic reviews, and meta-analyses to spot-check for references that may have been missed during the prior searches. The TF identified 22 additional articles by doing a spot-check for a total of 700 articles that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material. All abstracts were reviewed based on inclusion/exclusion criteria by 2 TF members. Any discrepancies between the reviewers were discussed and resolved by the chair or vice-chair. A total of 108 studies were determined to be suitable for meta-analysis and/or grading.

Statistical and meta-analysis and interpretation of clinical significance

Meta-analyses were performed on outcomes of interest, when possible, for each PICO question. For PICO 1, publications were categorized as either narcolepsy Type 1 ("NT1"), narcolepsy Type 2 ("NT2"), or unspecified narcolepsy ("narcolepsy"), based on the study inclusion criteria and patient characteristics. Comparisons of various interventions to no treatment were performed using data obtained from randomized controlled trials. Data included in this review include a mixture of change-from-baseline and final value scores. Both were used for meta-analysis of RCTs. The pooled results for each continuous outcome measure are expressed as the mean difference between the intervention and the comparator.

Table 1—PICO questions.

1	**Population:** Adult and pediatric patients diagnosed with narcolepsy type 1 or 2
	Intervention:
	Pharmacological therapy: anti-Parkinson's agent (amantadine), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), benzodiazepine receptor antagonist (flumazenil), benzodiazepines (temazepam, triazolam), central nervous system depressant (sodium oxybate), central nervous system stimulant (amphetamines and related preparations, armodafinil, caffeine, mazindol, methylphenidate and related preparations, modafinil), dietary supplement (L-carnitine), H3 receptor antagonist/inverse agonist (pitolisant), macrolide (clarithromycin), monoamine oxidase inhibitors/B (selegiline), norepinephrine reuptake inhibitor (atomoxetine), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin/norepinephrine reuptake inhibitor (venlafaxine), skeletal muscle relaxant (*R*-baclofen/baclofen), thyroid product (levothyroxine), tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, imipramine, maprotiline, nortriptyline, trimipramine), bupropion, light therapy, norepinephrine and dopamine reuptake inhibitor, and solriamfetol
	Behavioral therapy: exercise, scheduled naps/sleep extension, sleep hygiene, supportive care, trigger avoidance
	Immunotherapy: plasmapheresis, intravenous immunoglobulin, steroids
	Comparison: placebo, standard therapy, no treatment
	Outcome: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accidents/accident risk, work/school performance/attendance, fatigue, sleep quality
2	**Population:** Adult and pediatric patients diagnosed with idiopathic hypersomnia
	Intervention:
	Pharmacological therapy: anti-Parkinson's agent (amantadine), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), benzodiazepine receptor antagonist (flumazenil), benzodiazepines (temazepam, triazolam), central nervous system depressant (sodium oxybate), central nervous system stimulant (amphetamines and related preparations, armodafinil, caffeine, mazindol, methylphenidate and related preparations, modafinil), dietary supplement (L-carnitine), H3 receptor antagonist/inverse agonist (pitolisant), macrolide (clarithromycin), monoamine oxidase inhibitors/B (selegiline), norepinephrine reuptake inhibitor (atomoxetine), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin/norepinephrine reuptake inhibitor (venlafaxine), skeletal muscle relaxant (*R*-baclofen/baclofen), thyroid product (levothyroxine), tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, imipramine, maprotiline, nortriptyline, trimipramine), bupropion, light therapy, norepinephrine and dopamine reuptake inhibitor, and solriamfetol
	Behavioral therapy: exercise, scheduled naps/sleep extension, sleep hygiene, supportive care, trigger avoidance
	Immunotherapy: plasmapheresis, intravenous immunoglobulin, steroids
	Comparison: placebo, standard therapy, no treatment
	Outcome: excessive daytime sleepiness, disease severity, quality of life, work/school performance/attendance, cognitive performance, fatigue, sleep inertia
3	**Population:** adult and pediatric patients diagnosed with Kleine-Levin syndrome
	Intervention:
	Pharmacological therapy: anticonvulsant (carbamazepine, phenytoin, valproic acid), mood stabilizer (lithium carbonate), anti-Parkinson's agent (amantadine), antipsychotic (risperidone), benzodiazepine receptor antagonist (flumazenil), central nervous system stimulant (amphetamines and related preparations, armodafinil, methylphenidate and related preparations, modafinil), macrolide (clarithromycin), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin/norepinephrine reuptake inhibitor (venlafaxine), tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, imipramine, maprotiline, nortriptyline, trimipramine), bupropion, light therapy, norepinephrine and dopamine reuptake inhibitor, and solriamfetol
	Behavioral therapy: supportive care, trigger avoidance
	Comparison: placebo, standard therapy, no treatment
	Outcome: disease severity, quality of life, work/school performance/attendance, fatigue, mood
4	**Population:** adult and pediatric patients diagnosed with hypersomnia due to a medical disorder, including neurological disorders; adult and pediatric patients diagnosed with hypersomnia associated with a psychiatric disorder
	Intervention:
	Pharmacological therapy: anti-Parkinson's agent (amantadine), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), benzodiazepine receptor antagonist (flumazenil), benzodiazepines (temazepam, triazolam), central nervous system depressant (sodium oxybate), central nervous system stimulant (amphetamines and related preparations, armodafinil, caffeine, mazindol, methylphenidate and related preparations, modafinil), dietary supplement (L-carnitine), H3 receptor antagonist/inverse agonist (pitolisant), macrolide (clarithromycin), monoamine oxidase inhibitors/B (selegiline), norepinephrine reuptake inhibitor (atomoxetine), selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin/norepinephrine reuptake inhibitor (venlafaxine), skeletal muscle relaxant (*R*-baclofen/baclofen), thyroid product (levothyroxine), tricyclic antidepressants (amitriptyline, amoxapine, clomipramine, doxepin, imipramine, maprotiline, nortriptyline, trimipramine), bupropion, light therapy, norepinephrine and dopamine reuptake inhibitor, and solriamfetol
	Behavioral therapy: exercise, scheduled naps/sleep extension, sleep hygiene, supportive care, trigger avoidance
	Immunotherapy: plasmapheresis, intravenous immunoglobulin, steroids
	Comparison: placebo, standard therapy, no treatment
	Outcome: excessive daytime sleepiness, quality of life, work/school performance/attendance, difficulty waking in the morning, fatigue

Table 2—Outcomes by PICO question.

Outcomes	Patient Population				
	Narcolepsy	Idiopathic Hypersomnia	Kleine-Levin Syndrome	Hypersomnia Due to Medical Disorders	Hypersomnia Associated With Psychiatric Disorders
Accident risk	✓*				
Cataplexy	✓*				
Cognitive performance		✓			
Difficulty waking in the morning				✓	✓
Disease severity	✓*	✓*	✓*		
Excessive daytime sleepiness (EDS)	✓*	✓*		✓*	✓*
Fatigue	✓	✓	✓	✓	✓
Mood			✓		
Quality of life	✓*	✓*	✓*	✓*	✓*
Sleep inertia		✓			
Sleep quality	✓				
Work/school performance/attendance	✓*	✓*	✓*	✓*	✓*

*Critical outcomes.

Data from baseline and last-treatment time points from non-randomized trials were also compared. These are presented in a table format in the supplemental material. Data from crossover trials were treated as parallel groups. If data for multiple doses were available, then the mean and standard deviation (SD) were pooled. Some studies with a smaller sample size had data presented as a standard error (SE), and these data were converted into SD. Studies that reported data as median and interquartile range (IQR) were converted to means and SD for inclusion in meta-analyses.[17,18] If outcome data were not presented in the format necessary for statistical analysis (ie, mean, standard deviation, and sample size), or data were presented only in graphical formats, then the authors and study sponsors were contacted in an attempt to obtain the necessary data. If the necessary data were not available from the publication, the author, or ClinicalTrials.gov, then the paper was included in the evidence base as supporting evidence and the data were estimated and presented in a table in the supplemental material. These data were not used for meta-analysis or for determining the quality of evidence.

Meta-analyses were performed using Review Manager 5.3 software by pooling data across studies for each outcome measure. All analyses were performed using a random-effects model. Results from RCT(s) were displayed as a forest plot. Interpretation of clinical significance for the outcomes of interest was conducted by comparing the mean difference in effect of each treatment approach to the clinical significance threshold (CST; see **Table 3**). Standardized mean difference (SMD) was applied when the studies assessed the same outcome but measured it in a variety of ways. There was insufficient evidence to perform meta-analyses for some outcome measures. For some drugs, none of the accepted publications provided data that could be used for statistical analysis.

For adverse events, all data presented in the accepted papers were used for statistical and meta-analyses. Whenever possible, meta-analyses were performed by pooling data across studies for each outcome and adverse event. Meta-analyses for adverse events are presented as the risk difference. The risk difference is defined as the difference between the observed risks (proportions of individuals with the outcome of interest) in the 2 groups. It describes the actual difference in the observed risk of events between experimental and control interventions. Interpretation of adverse events was based upon the risk difference and clinical expertise of the TF.

GRADE assessment for developing recommendations

The evidence was assessed according to the GRADE process for the purposes of making clinical practice recommendations. The TF considered the following 4 individual GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use.[16,19]

1. Quality of evidence: Based on an assessment of the overall risk of bias (randomization, blinding, allocation concealment, selective reporting), imprecision (sample size < 100 or 95% confidence interval crosses the CST), inconsistency (I^2 cutoff of 50%), indirectness (study population), and risk of publication bias (funding sources), the TF determined their overall confidence that the estimated effect found in the body of evidence was representative of the true treatment effect that typical patients with any central disorder of hypersomnolence would experience. The TF determined the overall quality of the evidence for a given treatment based on the strength of evidence for all critical outcomes, relying exclusively on RCT data when

Table 3—Summary of clinical significance thresholds for critical and important outcome measures.

Outcome Tool	Clinical Significance Threshold*	Desired Change
Accident risk	10%	Decrease
Cataplexy	—	—
Diary-based daily/weekly episode frequency	25%	Decrease
Severity	25%	Decrease
Cognitive performance	—	—
Psychomotor vigilance test—reciprocal reaction time	10%	Increase
Difficulty waking in the morning	—	—
Varies	0.5 standardized mean difference	Decrease
Disease severity	—	—
CGI	1-point OR	Decrease
	33% of patients reporting change	Improvement
PGI	1-point OR	Decrease
	33% of patients reporting change	Improvement
Frequency and duration of symptoms	10%	Decrease
Number of d incapacitated	10%	Decrease
Other quantitative tools	10%	Improvement
Other qualitative tools	33% of patients reporting change	Improvement
Excessive daytime sleepiness	—	—
ESS	2 points	Decrease
ESS-CHAD	2 points	Decrease
MWT	2 min	Increase
MSLT	1 min	Increase
SSS	1 point	Decrease
Fatigue	—	—
FSS (global change)	0.5 points	Decrease
SF-36 energy/vitality subscale	3 points	Increase
BFI	0.3 points	Increase
FIS	4.8 points	Increase
MAF (global change)	5.0 points	Increase
Mood	—	—
BDI	5 points	Decrease
CDI	6 points	Decrease
PHQ-2	1 point	Decrease
PHQ-9	2 points	Decrease
Quality of life	—	—
FOSQ	1 point	Increase
PedsQL	1 point	Increase
SF-36	—	—
(Physical Component Summary)	3 points	Increase
(Mental Component Summary)	3 points	Increase
SF-12	4 points	Increase
Sleep inertia	—	—
Varies	0.5 standardized mean difference	Decrease
Sleep quality	—	—
PSQI	3 points	Decrease
PSG/actigraphy-based sleep efficiency (%)	10%	Increase

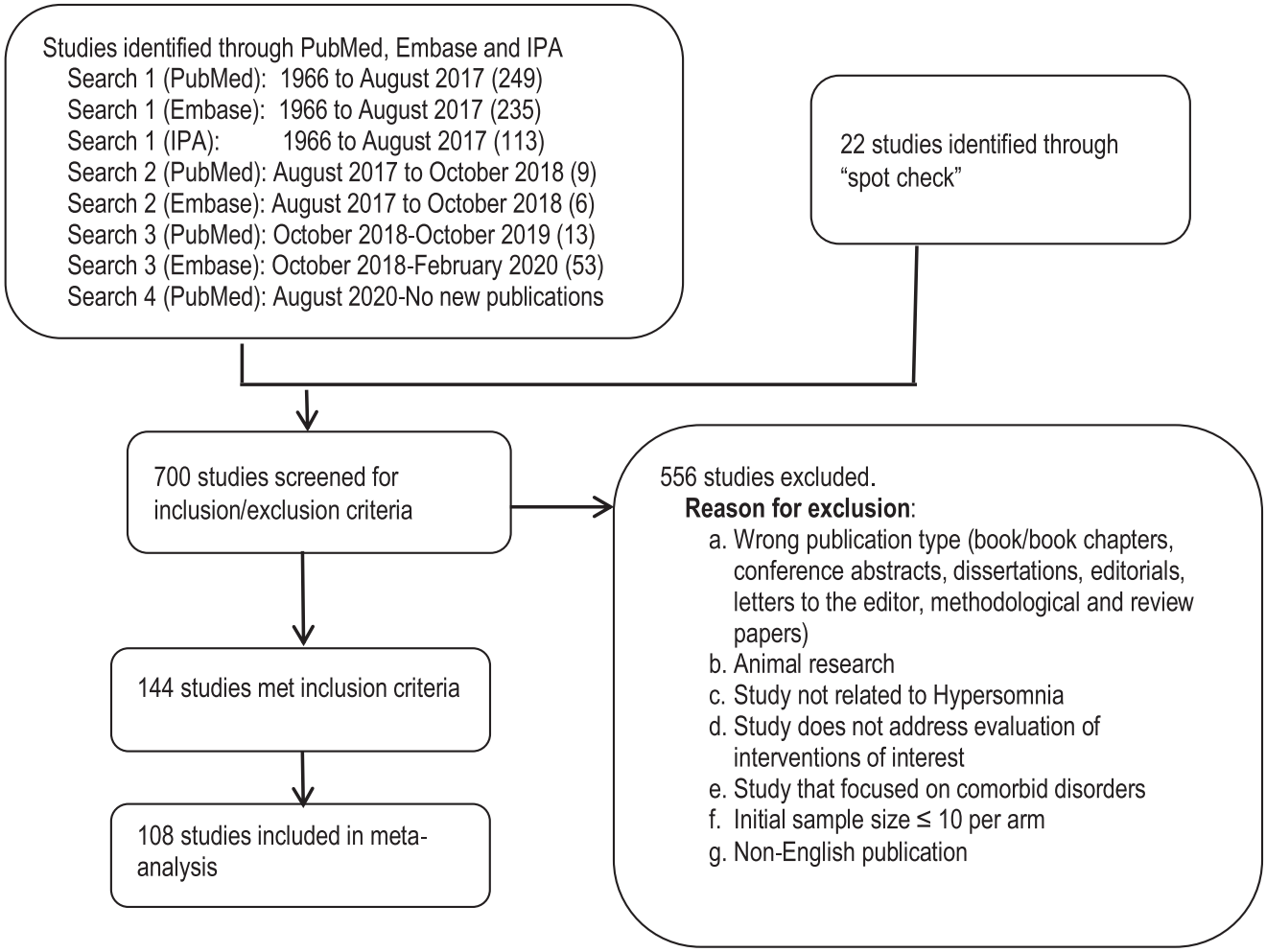
(continued on following page)

Table 3—Summary of clinical significance thresholds for critical and important outcome measures. (*Continued*)

Outcome Tool	Clinical Significance Threshold*	Desired Change
Work/school performance/attendance	—	—
Varies	0.5 standardized mean difference	Increase

*The clinical significance threshold applies to the comparison of posttreatment effects between intervention and placebo as well as a pre-/post treatment difference. BDI = Beck's Depression Inventory, BFI = Brief Fatigue Inventory, CDI = Children's Depression Inventory, CGI = Clinical Global Impression of change, ESS = Epworth Sleepiness Scale; ESS-CHAD = Epworth Sleepiness Scale for Children and Adolescents, FIS = Fatigue Impact Scale, FSS = Fatigue Severity Scale, FOSQ = Functional Outcomes of Sleep Questionnaire, MAF = Multidimensional Assessment of Fatigue, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, PGI = Patient Global Impression of change, PedsQL = Pediatric Quality of Life Inventory, PHQ-2 = Patient Health Questionnaire-2, PHQ-9 = Patient Health Questionnaire-9, PSG = polysomnography, PSQI- Pittsburgh Sleep Quality Index, SF-12 = 12-Item Short-Form Health Survey, SF-36 = 36-Item Short-Form Health Survey, SSS = Stanford Sleepiness Scale.

Figure 1—Evidence base flow diagram.



available. Important outcomes were not considered when determining the overall quality of evidence.

2. Benefits vs harms: Based on the meta-analysis (if data were available), analysis of any harms/side effects reported within the accepted literature, and the clinical expertise of the TF, the TF determined if the beneficial outcomes of the intervention outweighed any harmful side effects or vice versa. Black box warnings issued by the FDA to alert prescribers of the potential risk in prescribing a drug were taken into consideration.
3. Resource use: Based on the clinical expertise of the TF members, the TF judged resource use to be important for determining whether to recommend the use of a specific intervention for the treatment of central hypersomnia. When available, the TF used unit pricing obtained from the National Average Drug Acquisition Cost (NADAC).

The NADAC is designed to create a national benchmark that is reflective of the prices paid by retail community pharmacies to acquire prescription and over-the-counter covred outpatient drugs. Data are calculated by the Centers for Medicare & Medicaid Services (CMS).

4. Patient values and preferences: Based on the clinical expertise of the TF members and any data published on the topic relevant to patient preferences, the TF determined if patient values and preferences would be generally consistent across the majority of patients, and if patients would use the intervention based on the relative harms and benefits identified.

A summary of each individual GRADE domain is provided after the detailed evidence review for each intervention. Based on the clinical significance of the critical outcomes and an overall assessment of the individual GRADE domains described above, the TF determined the direction and strength of each recommendation statement (provided in the accompanying clinical practice guideline).[1,20]

Public comment and final approval

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 comments. The public comments and revised documents were submitted to the AASM Board of Directors, who subsequently approved the final documents for publication.

The AASM expects this systematic review to have an impact on professional prescribing behavior, improved patient outcomes, and, possibly, reduced health care costs. This review reflects the state of knowledge at the time of publication and will be reviewed and updated as new information becomes available.

THE TREATMENT OF NARCOLEPSY

The aim of the current literature review and data analyses was to focus on the treatment of narcolepsy. Because many studies included participants with NT1 and NT2 but did not separate effects between these 2 disorders, (a population called "unspecified narcolepsy" in this document), the TF chose to make combined recommendations for NT1 and NT2. Data below are presented by type of narcolepsy whenever available. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, resource use, and patient values and preferences that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. The interventions below are listed in alphabetical order.

Armodafinil

The review of the literature identified 1 randomized, double-blind, placebo-controlled trial[21] and 1 open-label flexible dose study[22] for the treatment of narcolepsy with armodafinil in patients with unspecified narcolepsy. The RCT (n = 196) assessed armodafinil in patients with narcolepsy at doses of 150 mg (n = 65) and 250 mg (n = 67) compared to placebo.[21]

The open-label study assessed armodafinil doses of 100–250 mg in 50 patients with unspecified narcolepsy.[22]

The figures and tables are provided in **Figure S1** and **Tables S1–S5** in the supplemental material. A summary of findings table is provided in **Table S6** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness (EDS), cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for quality of life or work/school performance.

Excessive daytime sleepiness: One RCT[21] assessed subjective sleepiness via changes based on the Epworth Sleepiness Scale (ESS). Data reported were not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

One open-label study of armodafinil (n = 28)[22] demonstrated a clinically significant pre-/post difference in the mean ESS score of 4.7 points lower (95% CI, 1.9–7.4 minutes lower) in patients with narcolepsy (type 1 or 2). Quality of evidence was very low due to imprecision (see **Table S1**).

One RCT: assessed improvement in objective sleepiness using the Maintenance of Wakefulness Test (MWT).[21] The mean change from baseline in the MWT score in the armodafinil group was an estimated 3.3 minutes higher (95% CI, 1.1–5.5 minutes higher) compared to placebo. Quality of evidence was moderate (see **Table S2**).

Cataplexy: One RCT[21] reported on the incidence of self-reported daily cataplexy episodes between any of the armodafinil dose groups and placebo as a change from baseline values. Data reported were not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

Disease severity: One RCT[21] used the 7-point clinical global impression of change (CGI-C) to assess change in illness compared with baseline during study visits. The proportion of patients with at least minimal improvement on the CGI-C rating from baseline to final visit in the armodafinil combined group was 71.0%, compared with 33.0% for placebo. The mean percentage improvement in CGI-C scores in the armodafinil group was 38.0% greater compared to placebo. Quality of evidence was high (see **Table S3**).

Accident risk: One RCT[21] reported on the diary-based mean reduction in the number of patients who reported mistakes, near misses, and accidents. The mean reduction in the number of patients reporting mistakes/accidents was 26.5% greater (improved) in the armodafinil group compared to the placebo.

The quality of evidence was moderate and was downgraded due to imprecision (see **Table S4**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality.

Fatigue: One RCT utilized the 9-item Brief Fatigue Inventory (BFI) to assess change in fatigue levels.[21] The mean BFI score in the armodafinil group was clinically significant at 1.1 points lower (95% CI, 0.5–1.7 points lower) compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S1**).

Sleep quality: One RCT[21] reported on the change in sleep quality based on sleep efficiency assessed by polysomnography. There was an insignificant improvement in sleep efficiency of 2.5% (95% CI, 1.3% lower–6.3% higher) in the armodafinil group when compared to placebo. Quality of evidence was high (see **Table S5**).

Overall quality of evidence

The TF determined that the overall quality of evidence for armodafinil to treat narcolepsy compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading of the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness and disease severity.[21]

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is likely in favor of armodafinil. The use of armodafinil demonstrated reductions in subjective and objective sleepiness, fatigue, and disease severity in patients with narcolepsy.

In patients with narcolepsy, most adverse events (AEs) were considered by the investigator to be mild or moderate in severity (defined as no or some limitation of usual activities), occurred with greatest frequency during the first 2 weeks of therapy, and were self-limiting.[21] Adverse events leading to withdrawal occurred in 7 patients with narcolepsy and consisted of "urticaria with angioedema" and "sleep disorder and urticaria," headache and depression, insomnia, diarrhea, disorientation with headache, dizziness, and abnormal behavior.

Across all RCTs included in the systematic review that reported on the use of armodafinil (irrespective of the indication), the risk difference between armodafinil and placebo for headache was 0.13 (95% CI, 0.03–0.20), indicating a greater risk of headache with armodafinil use[21,23] (see **Figure S66** in the supplemental material). Other commonly reported adverse events in the armodafinil group in the RCTs included nausea (10.7%), upper respiratory tract infection (9%), and dizziness (8.4%).[21,23] Commonly reported adverse events across all observational studies on the use of armodafinil included headache (24.2%), sinusitis (10.2%), somnolence (10.2%), anxiety (8.1%), nausea (8.1%), and nasopharyngitis (8.1%).[22,24] The more serious but rare AEs reported in product information for armodafinil, such as Stevens-Johnson syndrome, were not detected in the individual studies. The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of armodafinil in pregnancy.

Resource use

Per the NADAC database, the unit cost of 50 and 250 mg tablets ranged from $0.26–$1.18.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was no uncertainty or variability in how much people value the main study outcomes and that the majority of patients would probably use armodafinil when compared to no treatment for their narcolepsy.

Clomipramine

TF review of the literature identified a single retrospective observational long-term self-reported study in 16 patients with NT1 on clomipramine alone (dosage range, 25–125 mg; mean dosage, 49 mg/24 hours).[27]

The data table is provided in **Table S7** in the supplemental material. A summary of findings table is provided in **Table S8** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. The study identified in our literature review did not report data or did not use a validated assessment scale for cataplexy, disease severity, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: One observational study reported on changes in sleepiness using the ESS score.[27] The mean pre-/post difference in ESS in adult patients on clomipramine was clinically significant at 3.2 points lower (95% CI, 0.1–6.3 points lower). The quality of evidence was very low due to imprecision (see **Table S7**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep

quality. The study identified in our literature review did not report data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for clomipramine to treat narcolepsy was very low based on the critical outcomes reported in the literature and downgrading of the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcome: excessive daytime sleepiness.

Benefits and harms

The TF concluded that the overall balance between the desirable effect on excessive daytime sleepiness and undesirable effects probably was inconclusive. Clomipramine is typically prescribed for the treatment of cataplexy, but the TF did not have data from validated cataplexy measures to assess the efficacy of this agent as an anticataplectic treatment.

The use of clomipramine demonstrated mild reduction in subjective sleepiness in patients with narcolepsy. The adverse events reported included dry mouth (38%), constipation (25%) and impaired sexual potency or delayed ejaculation (19%) in patients on clomipramine.[27] This drug has a black box warning for increased suicidality risk in children, adolescents, and young adults with major depressive or other psychiatric disorders.

The balance of risks and harms is likely different for pregnant and breastfeeding women. Based on animal data, clomipramine may cause fetal harm. Human data are insufficient to determine risk.

No other studies included in the systematic review reported on the use of clomipramine (irrespective of the indication).

Resource use

At the time of this publication, per the NADAC database, the unit cost of 25–50 mg doses ranged from $3.49–$3.41 for each capsule.[26] Medication cost to any given patient is uncertain and is determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that the majority of patients with narcolepsy would probably not use this medication given the relatively high frequency of mild to moderate symptoms.

Dextroamphetamine

The TF identified 3 studies focused on dextroamphetamine in their literature review.[27–29] One was a randomized, double-blind, placebo-controlled study of both levo-amphetamine (20–60 mg) and dextroamphetamine (10–45 mg) that compared these drugs to each other and placebo in 12 patients with NT1 and NT2.[28] Another one was an observational, single-blind study assessing the effect of dexamphetamine sulfate (10 and 30 mg/day) and dexedrine spansules (10 mg) in 20 patients with NT1 and NT2 over a 4-week period.[29]

The third study was a single retrospective observational long-term self-reported study case series investigating episodes of sleepiness and cataplexy in 60 patients with NT1 on dexamphetamine alone (dosage range, 5–60 mg; mean dosage, 16 mg/24 hours).[27]

The data tables are provided in **Table S9** and **Table S10** in the supplemental material. A summary of findings table is provided in **Table S11** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for disease severity, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: One observational study reported on changes in sleepiness in patients with unspecified narcolepsy on dextroamphetamine using the ESS score.[27] It demonstrated a clinically significant pre-/post difference in the mean ESS score of 5.0 points lower (95% CI, 3.4–6.6 points lower). The quality of evidence was determined to be very low due to imprecision (see **Table S9**).

Cataplexy: One observational single-blind study reported on changes in the daily cataplexy episode rate in patients with unspecified narcolepsy.[29] The study showed a 33% difference in the daily cataplexy rate pre- and post-dextroamphetamine use, a clinically significant finding. The quality of evidence was determined to be very low due to imprecision (see **Table S10**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for dextroamphetamine for the treatment of narcolepsy was very low based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness and cataplexy.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects was likely in favor of dextroamphetamine. The use of dextroamphetamine improved sleepiness and level of alertness.

In patients with narcolepsy, the most common side effects were attributed to long-term drug treatment. In the RCT, commonly reported adverse events in the dextroamphetamine group included sweatiness (25%) and edginess (30%).[28] In the observational studies, commonly reported adverse events included weight gain (21%), irritability (16%), decreased appetite (16%), sleepiness (13%), and dry mouth (13%). This

medication can specifically cause problems with sleep onset if taken later in the day.[27,29]

No other studies included in the systematic review reported on the use of dextroamphetamine. (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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 that prolonged administration may lead to dependence. Based on animal data, dextroamphetamine may cause fetal harm. Human data are insufficient to determine risk. Particular attention should be paid to the possibility of patients obtaining amphetamines for nontherapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.[30]

Resource use

The medication is available in tablet, capsules, spansules, and liquid forms. At the time of this publication, per the NADAC database, the unit cost of 5–15 mg doses ranged from $1.40–$1.80 for each unit.[26] Costs are likely to vary and are determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was probably no important uncertainty or variability in how much people value the main outcomes of these studies and that the majority of patients would probably use dextroamphetamine for narcolepsy when compared to no treatment. The medication is generally effective and well-tolerated.

L-carnitine

The TF identified a single randomized, double-blind, crossover, and placebo-controlled trial of L-carnitine (510 mg/day) of 16 weeks' duration in 28 patients with NT1.[31]

The data figures are provided in **Figures S2–S4** in the supplemental material. A summary of findings table is provided in **Table S12** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. The study identified in our literature review did not report data for disease severity, accident risk, or work/school performance.

Excessive daytime sleepiness: One RCT reported on changes in sleepiness scores using the Japanese Epworth Sleepiness Scale (JESS).[31] The mean JESS score in the L-carnitine group was not clinically significant at 0.0 points higher (95% CI, 2.0 lower–2.0 points higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S2**).

Cataplexy: One RCT reported on changes in daily cataplexy rates.[31] Data reported were not suitable for analysis.

Quality of life: One RCT reported on quality of life using the mental health summary score of the SF-36 tool. The mean SF-36 mental health summary scores in patients with NT1 in the L-carnitine group were not clinically significant at 0.5 points higher (95% CI, 3.5 points lower–4.5 points higher) compared to placebo.[31] Quality of evidence was low due to serious imprecision (see **Figure S3**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. The study identified in our literature review did not report data for sleep quality.

Fatigue: One RCT reported on fatigue using the vitality subscale of the SF-36. The mean SF-36 energy/vitality component score in the L-carnitine group was 2.0 points higher (95% CI, 3.5 points lower–7.5 points higher) compared to placebo. This result was not clinically significant. Quality of evidence was low due to serious imprecision (see **Figure S4**).

Overall quality of evidence

The TF determined that the overall quality of evidence to treat patients with NT1 with L-carnitine compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects probably did not favor the use of L-carnitine as both the desirable and undesirable outcomes were trivial.

The use of L-carnitine resulted in an insignificant clinical effect on sleepiness in patients with NT1. However, L-carnitine was well tolerated with no side effects observed.[31]

No other studies included in the systematic review reported on the use of L-carnitine (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women. Animal studies have not shown fetal harm. Human data are insufficient to determine risk.

Resource use

This medication is available over the counter as a nonpharmacologic oral diet supplement. Medication cost is uncertain.

Patient values and preferences

The TF felt that there was probably no important uncertainty or variability in how people value the main outcomes, but there were insufficient data to determine patient values for or against treatment. The JESS was felt to be a reasonable approximation of the ESS. The medication had no effect on subjective sleepiness as determined by the Japanese ESS and only modest reductions in subjective total nap time. No treatment effect was observed for quality of life or fatigue.

Methylphenidate

The TF's review of the literature identified 2 observational studies examining the efficacy of methylphenidate in the treatment of unspecified narcolepsy. One was a prospective cohort study in 11 patients (mean dose 43 mg).[32] The other observational study looked at the treatment efficacy of methylphenidate in 13 patients (mean dose 33.3 mg).[33]

The TF also identified 1 case series of 106 patients with unspecified narcolepsy treated with 10–60 mg of methylphenidate.[34]

The data tables are provided in **Table S13** and **Table S14** in the supplemental material. A summary of findings table is provided in **Table S15** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for cataplexy, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: One observational study reported on the ability to maintain wakefulness in patients with unspecified narcolepsy on methylphenidate. It demonstrated a clinically significant pre-/post difference in the mean MWT score of 2.9 minutes higher (95% CI, 2.0 minutes lower–7.8 minutes higher). The quality of evidence was determined to be very low due to serious imprecision[33](see **Table S13**).

A separate observational prospective cohort study also reported on the ability to maintain wakefulness in patients with unspecified narcolepsy on methylphenidate.[32] The study reported a mean MWT posttreatment score in the methylphenidate group of 18.4 minutes. Data reported were not suitable for analysis.

Disease severity: The case series study reported on improvement in disease severity using the Global Improvement Rating (GIR) scale.[34] As the mean daily dose of methylphenidate was increased from 10–60 mg, moderate or marked improvement on the GIR was noted in 89.7% of the patients, which was clinically significant. Quality of evidence was determined to be very low due to imprecision (see **Table S14**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF agreed that that the overall quality of evidence for methylphenidate for the treatment of narcolepsy was very low based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness and disease severity.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects was likely in favor of methylphenidate. The use of methylphenidate for the treatment of narcolepsy showed improvement in disease severity.

In patients with narcolepsy, the most commonly reported side effects were loss of appetite and headache.

Across all RCTs included in the systematic review that reported on the use of methylphenidate (irrespective of the indication), most adverse events in the methylphenidate group were mild and included loss of appetite (20%), nausea (10%), vomiting (10%), and palpitations (10%).[35] Commonly reported adverse events reported across all observational studies on the use of methylphenidate included dry mouth (38.6%), sweating (34.9%), headache (24.5%), stomach discomfort (21.6%), and loss of appetite (16.9%).[34] The balance of risks and harms is likely different for pregnant and breastfeeding women.

In addition, this drug 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. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Based on animal data, methylphenidate may cause fetal harm. Human data are insufficient to determine risk. Caution should be exercised if administered to nursing mothers.[36]

Resource use

At the time of this publication, the NADAC reported the drug's pricing ranged from $0.14/mL for solution, $0.12–$2.50/tablet (5–20 mg), and $1.95–$3.51/capsule (10–60 mg).[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was possibly important uncertainty about or variability in how much people value the main outcomes of these studies because the disease severity measure was unstandardized but seemed consistent with the validated patient global impression scale. The medication is effective and reasonably well tolerated. Side effects are manageable. Thus, it is likely that the majority of patients would probably use methylphenidate when compared to no treatment.

Modafinil

The TF identified 2 RCTs assessing the efficacy of modafinil treatment for adult patients with NT1 compared to placebo[37,38] and 1 observational study of modafinil efficacy among adult patients with NT1.[39] Sample sizes ranged from 19–45, and the modafinil dose ranged from 200–400 mg/day.

The TF did not find any modafinil treatment studies assessing efficacy among patients with NT2 specifically.

The TF identified 7 RCTs for the treatment of unspecified narcolepsy with modafinil vs placebo.[40–46] Four observational

studies of modafinil use in patients with unspecified narcolepsy had sample sizes ranging from 38–471 and study durations ranging from 5–40 weeks.[47–50]

The meta-analyses and figures and tables are provided in **Figures S5–S11** and **Tables S16–S25** in the supplemental material. A summary of findings table is provided in **Table S26** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for accident risk or work/school performance.

Excessive daytime sleepiness: One RCT assessed the efficacy of modafinil treatment on excessive daytime sleepiness using the Stanford Sleepiness Scale (SSS) for adult patients with NT1.[38] The study demonstrated a clinically significant difference of 1.3 points lower (95% CI, 0.6–2.0 points lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S5**).

One observational study assessed the effects of modafinil on excessive daytime sleepiness in patients with NT1 using the ESS.[39] The mean ESS score range of pre-/post differences on modafinil was a clinically significant 2.2 points lower (95% CI, 0.9–3.6 points lower), supporting the findings of the RCT. The quality of evidence was very low due to imprecision. (see **Table S16**).

Five RCTs and 2 crossover trials evaluated the effect of modafinil on excessive daytime sleepiness for the treatment of unspecified narcolepsy using the ESS.[40–46] Doses ranged from 200–600 mg/day. The meta-analyses demonstrated a clinically significant reduction of 2.8 points (95% CI, 1.7–3.8 points lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S6**).

In addition, 3 observational studies of modafinil assessed the effects of modafinil on excessive daytime sleepiness among patients with unspecified narcolepsy using the ESS.[48,50,51] Pre-/post difference results could only be reported for 2 of the studies[48,51] because the third study[50] did not report pre-modafinil treatment parameters. The mean ESS score pre-/post difference in these patients ranged from 0.9–4.1 points lower. The quality of evidence was very low due to imprecision (see **Table S17**).

Five RCTs and 2 crossover trials evaluated the effect of modafinil on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT.[40–46] The mean MWT score in the modafinil group was a clinically significant 4.1 minutes higher (95% CI, 3.4–4.8 minutes higher) compared to placebo. The quality of evidence was high (see **Figure S7**).

The TF identified 1 RCT that evaluated the effect of modafinil on the ability to maintain wakefulness in patients with NT1 using the MWT.[37] Since the data were only available in a graphical format in the publication, they were not combined with the meta-analyses. The estimated mean MWT score in the modafinil group was calculated as 2.1 minutes higher (95% CI, 0.4 minutes lower–4.6 minutes higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Table S18**).

The TF identified 2 RCTs that compared the effect of modafinil to placebo for assessment of sleepiness by using the MSLT in patients with unspecified narcolepsy.[45,46] The mean MSLT score in patients on modafinil was 1.6 minutes higher (95% CI, 0.9–2.2 minutes higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S8**).

Cataplexy: One RCT reported on daily cataplexy episodes in patients with unspecified narcolepsy,[41] although patients presumably had NT1. The percentage difference in cataplexy reduction was 25.7%, which is clinically significant. The quality of evidence was downgraded to moderate due to imprecision (see **Table S19**).

A crossover RCT reported on daily cataplexy episodes in patients with NT1 on modafinil.[37] There were no baseline data on the daily cataplexy episodes and so it was not feasible to calculate the percentage reduction. The study mentioned the absence of any significant effect of modafinil on cataplexy. The data presented were not sufficient to evaluate the clinical significance of the findings.

Disease severity: One RCT reported the overall disease severity in patients with NT1 as measured by the Clinical Global Index (CGI).[37] It demonstrated a clinically insignificant mean difference of 0.3 points lower (95% CI, 0.71 points lower–0.13 points higher) The quality of evidence was downgraded to low due to serious imprecision (see **Figure S9**).

Two RCTs evaluated disease severity in adult patients with unspecified narcolepsy as measured by the CGI-C. The percentage of patients reporting an improvement ranged from 19%–72% in the modafinil group compared to placebo[44,45] (see **Table S20**).

Another RCT[41] reported that the patients randomized to modafinil treatment had an 86% improvement in CGI-EDS over placebo, which was clinically significant. The same RCT also reported a 29% improvement in CGI-C for cataplexy, which was not clinically significant. The quality of evidence was downgraded in both instances to moderate due to imprecision (see **Tables S21** and **S22**)

Quality of life: One RCT utilized the SF-36 (physical and mental summary components) to assess treatment efficacy with modafinil vs placebo in patients with unspecified narcolepsy.[52] The physical health summary component was 0.5 points higher (95% CI, 1.2 points lower–2.2 points higher) compared to placebo and this did not meet the threshold for clinical significance. The quality of evidence was high (see **Figure S10**).

The mental health summary component demonstrated a clinically significant mean difference of 3.5 points higher (95% CI, 1.8–5.2 points higher).[52] The quality of evidence was downgraded to moderate due to imprecision (see **Figure S10**).

Two observational studies to assess treatment efficacy with modafinil vs placebo in patients with unspecified narcolepsy showed a greater benefit of modafinil on the mental health domain compared to the physical health domain on the SF-

36.[47,48] The mean SF-36 physical health summary component pre-/post difference ranged from 1.3–2.3 points higher. The quality of evidence was low (see **Table S23**).

The mean SF-36 mental health summary component pre-/post difference ranged from 3.0–4.4 points higher.[47,48] The quality of evidence was low (see **Table S24**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality.

Fatigue: One RCT utilized the SF-36 (energy and vitality component) to assess fatigue with modafinil vs placebo in patients with unspecified narcolepsy.[52] The mean SF-36-energy and vitality component in the modafinil group demonstrated a clinically significant 8.0 points higher (4.3–11.7 points higher) compared to placebo. The quality of evidence was high (see **Figure S11**).

Two observational studies also showed a benefit on the SF-36 vitality score in patients with unspecified narcolepsy.[47,48] They demonstrated a pre-/post difference range of 13.0–19.5 points higher. The quality of evidence was low (see **Table S25**).

Sleep quality: One RCT[53] reported on sleep quality in a post-hoc analysis of responses to a single question on the Pittsburgh Sleep Quality Index (PSQI) that asks, "During the past month, how would you rate your sleep quality overall?" with responses of 0 denoting "very good" to 3 denoting "very bad." This publication did not provide data that were sufficient to derive a conclusive clinical significance. Quality of evidence was also not assessed.

Overall quality of evidence

The TF determined that the overall quality of evidence for modafinil to treat narcolepsy compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness, cataplexy, disease severity, and quality of life.

Benefits and harms

The TF determined that the benefits of modafinil use in patients with unspecified narcolepsy outweighed the risks and adverse events reported in the trials.

In patients with narcolepsy, the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: nausea: 0.06 (95% CI, 0.03–0.10), diarrhea: 0.04 (95% CI, 0.00–0.07), headache: 0.03 (95% CI, –0.02 to 0.08), anxiety or nervousness: 0.03 (95% CI, –0.01 to 0.06), and dry mouth: –0.02 (95% CI, –0.07 to 0.12).[44,46,49,51,54]

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth: –0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06;[44,46,51,54–62] see **Figures S67–S75** in the supplemental material). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

In general, cost-effectiveness analyses have demonstrated that modafinil is a cost-effective therapy compared to no therapy. At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients with narcolepsy would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment and is based on modafinil's efficacy to reduce daytime sleepiness and its relatively mild side effects. For the most part, the TF determined that patients would likely accept the small risk of AEs for this benefit.

Naps (scheduled)

The TF literature review identified 1 observational study that investigated the effectiveness of nap therapy for adult patients with narcolepsy.[66] Sixteen patients with unspecified narcolepsy were enrolled in a monthlong program of 3 regularly scheduled 15-minute naps.

The table is provided in **Table S27** in the supplemental material. A summary of findings table is provided in **Table S28** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease

severity, quality of life, accident risk, and work/school performance. The study identified in our literature review did not report data for cataplexy, disease severity, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: The observational study recorded MWT determined excessive daytime sleepiness in response to nap therapy in adult patients with unspecified narcolepsy.[66] The mean MWT pre-/post difference in the naps group was 2.6 minutes higher (95% CI, 1.5 minutes lower–6.7 minutes higher). This met the threshold for clinical significance. The quality of evidence was downgraded to very low due to imprecision (see **Table S27**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. The study identified in our literature review did not report data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the quality of evidence for the treatment of excessive daytime sleepiness with naps alone was very low based on the critical outcome reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcome: excessive daytime sleepiness.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is likely in favor of naps. Naps improved the ability to maintain wakefulness in patients with unspecified narcolepsy. There were no side effects noted.

No other studies included in the systematic review reported on the use of naps (irrespective of the indication).

Resource use

In general, there are no direct costs. Work schedules and policies may contribute to indirect costs.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcome and concluded that the majority of patients would likely be in favor of naps. There were insufficient data to determine patient values for or against treatment. Naps may not be feasible, based upon the nature of work/school schedules and work/school environment.

Pitolisant

The TF identified 1 randomized, double-blind trial examining the effect of pitolisant (n = 31) vs placebo (n = 30) vs modafinil (n = 33) on sleepiness, daily cataplexy rate, and disease severity in patients with unspecified narcolepsy.[41] Treatment lasted 8 weeks, including 3 weeks of flexible dosing (pitolisant 10, 20, and 40 mg doses; modafinil 100, 200, and 400 mg doses) followed by 5 weeks of stable dosing.

Another randomized double-blind trial included patients with NT1 and examined the effect of pitolisant (n = 54) vs placebo (n = 51) on sleepiness, weekly cataplexy rates, and disease severity.[67]

The literature search also identified 1 placebo controlled crossover study of 22 patients with NT1 treated with 40 mg of tiprolisant (former name for pitolisant).[68]

All 3 studies were industry funded.[41,67,68] Data for outcomes—Epworth Sleepiness Scale scores, the MWT, rates of cataplexy, and the CGI-C for cataplexy from 2 studies[41,67] were obtained from personal communication via email correspondence with Craig Davis (PsyD, Senior Medical Director, Medical Affairs, Harmony Biosciences, LLC, June 2019). Details of data obtained from this communication are included in the supplemental material.

The figures and tables are provided in **Figures S12–S17** and **Tables S29–S32** in the supplemental material. A summary of findings table is provided in **Table S33** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: Two RCTs evaluated the effect of pitolisant on excessive daytime sleepiness in patients with NT1 using the ESS.[67,68] Meta-analysis showed a clinically significant improvement of 3.8 points lower (95% CI, 2.0–5.5 points lower) compared to placebo. The quality of evidence was high (see **Figure S12**).

Another RCT evaluated the effect of pitolisant on excessive daytime sleepiness in patients with unspecified narcolepsy using the ESS.[41] The mean ESS score in the pitolisant group demonstrated a clinically significant reduction of 3.6 points (95% CI, 0.9–6.3 points lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S13**).

One RCT (n = 61) evaluated the effect of pitolisant on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT.[41] There was a clinically significant mean MWT score of 2.1 minutes higher (95% CI, 0.6–3.6 minutes higher) in the pitolisant group compared to placebo. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S14**).

Another RCT evaluated the effect of pitolisant on the ability to maintain wakefulness in patients with NT1 using the MWT.[67] The mean MWT score in the pitolisant group was clinically significant at 4.3 minutes higher (95% CI, 0.5 minutes lower–9.1 minutes higher) compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S15**).

Cataplexy: One RCT[41] evaluated the change in daily cataplexy episodes in patients with unspecified narcolepsy. The mean

reduction in daily cataplexy rates in the pitolisant group was 65.4% compared to 9.3% in the placebo group. There was a clinically significant 56.1% reduction. The quality of evidence was moderate due to imprecision (see **Table S29**).

Another RCT evaluated the change in weekly cataplexy episodes in patients with NT1.[67] The mean reduction in weekly cataplexy rates in the pitolisant group was 75% compared to 38% in the placebo group. There was a clinically significant 37% reduction. The quality of evidence was high (see **Table S30**).

Disease severity: One RCT evaluated the disease severity using the CGI-C on cataplexy in patients with unspecified narcolepsy.[41] The mean CGI-C on the cataplexy score in the pitolisant group was a clinically insignificant 0.5 points lower (95% CI, 1.3 points lower–0.3 points higher) when compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S16**).

The above RCT also evaluated the disease severity using the CGI-C on sleepiness in patients with unspecified narcolepsy.[41] There was an improvement in 17% of patients on pitolisant when compared to placebo. This was not clinically significant. The quality of evidence was moderate due to imprecision (see **Table S31**).

Another RCT evaluated disease severity using the CGI-C on cataplexy as above in patients with NT1.[67] The mean CGI-C on the cataplexy score in the pitolisant group was not clinically significant at 0.9 points lower (95% CI, 1.3–0.5 points lower) when compared to placebo. Quality of evidence was moderate due to imprecision (see **Figure S17**).

This NT1-specific RCT also evaluated the disease severity using the CGI-C on EDS.[67] There was an improvement in 45% of patients on pitolisant when compared to placebo, which is a clinically significant change. The quality of evidence was high (see **Table S32**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for pitolisant for the treatment of narcolepsy compared to placebo was high based on the critical outcomes reported in the literature. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness, cataplexy, and disease severity.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is in favor of pitolisant. The intervention demonstrated reductions in subjective and objective measures of sleepiness and cataplexy when compared to placebo.

In patients with narcolepsy, the risk difference of the commonly reported adverse effects between pitolisant and placebo were as follows: nausea: 4.9 (95% CI, 0.98–24.12), headache: 0.12 (95% CI, –0.05 to 0.28), and insomnia: 0.09 (95% CI, 0.01–0.18). None of them resulted in treatment cessation. Four AEs were considered severe: abdominal discomfort, nausea, malaise, and insomnia[41,67,68] (see **Figures S76–S78** in the supplemental material). One observational study reported the following adverse events (in patients with idiopathic hypersomnia): gastrointestinal pain (15.4%), increased appetite and weight gain (14.1%), headache (12.8%), insomnia (11.5%), and anxiety (9%).[69] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Pitolisant has low abuse potential and thus is not a scheduled federally controlled substance. Based on animal data, pitolisant may cause fetal harm. Human data are insufficient to determine risk. 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.[70]

Resource use

As pitolisant has just been approved by the FDA, at the time of this publication, there are no available cost data in the NADAC database. Other than medication cost, there should be no other substantive resource requirement for pitolisant over and above other narcolepsy treatments. This drug is only available through specialty pharmacies. The monotherapeutic aspect of this medication may reduce costs in the long-term compared to separate treatments for sleepiness and cataplexy for some patients with NT1. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was no uncertainty or variability in how much people value the main outcomes, and the majority of patients would likely use pitolisant when compared to no treatment. Pitolisant provides a monotherapy option for patients with narcolepsy, and most patients would likely prefer to take a single medication, when possible. Medication cost, side effects, and drug-drug interactions support this approach. Both adverse effects and serious adverse effects were similar to other narcolepsy treatments. This assessment reflects the TF's clinical judgment, based on pitolisant's ability to improve sleepiness and cataplexy and its relatively benign side effect profile.

Selegiline

The review of the literature identified 2 double-blind placebo-controlled crossover studies[71,72] and 1 observational prospective cohort study examining the efficacy of selegiline in the treatment of narcolepsy.[32] One study included 17 patients with unspecified narcolepsy and doses of 10, 20, 30, or 40 mg of selegiline over a 4-week period.[71] Another study assessed doses of 10 and 20 mg of selegiline in 30 patients with unspecified narcolepsy,[72] and a third study examined 11 patients with unspecified narcolepsy taking 15–30 mg of selegiline.[32]

The figure is provided in **Figure S18** in the supplemental material. A summary of findings table is provided in **Table S34** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for disease severity, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: One RCT compared the effect of selegiline to placebo for assessment of sleepiness by using the MSLT. The mean MSLT score in the selegiline group was 1.4 minutes higher (95% CI, 0.1 minutes lower–3.0 minutes higher), indicating a clinically significant improvement with selegiline.[72] The quality of evidence was rated moderate due to imprecision (see **Figure S18**).

An open-label study evaluated the effect of selegiline on the ability to maintain wakefulness in patients with narcolepsy using the MWT.[32] The mean MWT posttreatment score in the selegiline group was 9.4 minutes (95% CI, 6.6–12.2 minutes). A lack of pretreatment data prevented the TF from determining clinical significance in improvement on treatment. Quality of evidence was also not assessed.

Cataplexy: A double-blind placebo-controlled crossover study reported on the mean number of weekly cataplexy attacks.[71] The study mentions that the number of cataplectic attacks was decreased in a dose-dependent manner. However, data reported were not suitable for analysis and not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

Another RCT reported a 50% reduction in cataplexy rate in patients on selegiline (20 mg).[72] Data reported were not suitable for analysis and not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

One observational study reported that 50% of the enrolled patients with cataplexy reported symptom improvement on selegiline (up to 30 mg/day).32 Data reported were not suitable for analysis and not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for selegiline for the treatment of narcolepsy compared to placebo was moderate based on the critical outcomes reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcome: excessive daytime sleepiness.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects was inconclusive. The literature reviewindicated improved sleepiness in patients with narcolepsy on selegiline. The intervention demonstrated moderate undesirable effects.

In patients with narcolepsy, most adverse events were considered moderate. Commonly included adverse events reported in the RCTs included headache, dry mouth, insomnia, sweating, and muscle twitching. Commonly reported adverse events reported in the observational studies on the use of selegiline included headache, irritability, and dry mouth.

Across all RCTs included in this systematic review that reported on the use of selegiline (irrespective of the indication), side effects in the selegiline group included irritability (20%), slight difficulty in micturition (10%), and headache (10%). The adverse events required neither treatments nor the interruption of the study drug. Commonly reported adverse events reported in 1 observational study on the use of selegiline included headache (13%) and irritability (5%).[32] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, selegiline is a monoamine oxidase-B inhibitor and should not be taken with medications (eg, SSRIs) that could result in serotonin syndrome. Based on animal data, selegiline may cause fetal harm. Human data are insufficient to determine risk. Monoamine oxidase inhibitors (MAO-Is) have considerable risk associated with a black box warning related to suicidal thoughts and behaviors in children, adolescents, and young adults and hypertensive crisis when interacting with many antidepressant medications.

Resource use

At the time of this publication, per the NADAC database, the unit cost of a 5 mg tablet/capsule was $1.17.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was probably no important uncertainty or variability in how patients value the critical outcome. There were insufficient data to determine patient values for or against treatment with regard to critical outcomes of cataplexy and excessive daytime sleepiness as measured by MWT. Side effects are potentially serious when combined with other medications.

Sodium oxybate

The TF identified 1 RCT that examined the effect of sodium oxybate vs placebo in patients with unspecified narcolepsy[44] and 5 RCTs that examined the effect of sodium oxybate in patients with NT1.[73–77] Sample sizes ranged from 20–228. The sodium oxybate dose ranged from 3–9 g.

The TF identified 3 observational studies that examined the effect of sodium oxybate vs placebo in patients with unspecified narcolepsy[78–80] and 3 studies that examined the effect of sodium oxybate in patients with NT1.[81–83] The initial dose of

sodium oxybate ranged from 3–4.5 g and increased if clinically indicated to a maximum of 9 g over several weeks.

The meta-analyses and figures and tables are provided in **Figures S19–S23** and **Tables S35–S47** in the supplemental material. A summary of findings table is provided in **Table S48** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for accident risk or work/school performance.

Excessive daytime sleepiness: One RCT evaluated the effect of sodium oxybate on excessive daytime sleepiness in patients with unspecified narcolepsy using the ESS.[44] This study demonstrated a clinically significant reduction of 3.3 points (95% CI, 1.2–5.4 points lower) when compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S19**).

Two RCTs evaluated the effect of sodium oxybate on excessive daytime sleepiness in patients with NT1 using the ESS.[74,75] The meta-analysis showed a clinically insignificant reduction of 1.5 points (95% CI, 0.6–2.4 points lower) when compared to placebo. The quality of evidence was high (see **Figure S20**).

One observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with unspecified narcolepsy using the ESS.[78] There was a clinically significant mean ESS pre-/post difference score of 5.9 points lower (95% CI 4.5–7.2 points lower). The quality of evidence was very low due to serious imprecision (see **Table S35**).

Two observational studies assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with NT1 using the ESS.[81,82] There was a clinically significant pre-/post range reduction in the mean ESS score for patients on sodium oxybate of 3.8–3.9 points lower, supporting the findings of the RCTs. The quality of evidence was very low due to imprecision (see **Table S36**).

One RCT compared the effect of sodium oxybate to placebo for assessment of sleepiness by using the MSLT in patients with NT1.[73] The mean MSLT score on sodium oxybate was not clinically significant at 0.7 minutes higher (95% CI, 0.4 minutes lower–1.8 minutes higher) compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S21**).

One observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with NT1 using the MSLT.[82] The mean MSLT score pre-/post difference in these patients was a clinically insignificant 0.4 minutes higher (95% CI, 1.2 minutes lower–2.0 minutes higher). The quality of evidence was very low due to serious imprecision (see **Table S37**).

Another observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with unspecified narcolepsy using the MSLT.[79] The mean MSLT score pre-/post difference in these patients was a clinically significant 1.5 minutes higher (95% CI, 0.3 minutes lower–3.4 minutes higher). The quality of evidence was very low due to imprecision (see **Table S38**).

One RCT evaluated the effect of sodium oxybate on the ability to maintain wakefulness in patients with NT1 using the MWT.[74] The mean MWT change from baseline score in patients with NT1 on sodium oxybate was clinically significant 3.8 minutes higher (95% CI, 1.2–6.4 minutes higher). The quality of evidence was high (see **Figure S22**).

One RCT evaluated the effect of sodium oxybate on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT.[44] The mean MWT score in patients with narcolepsy on sodium oxybate was a clinically significant 5.1 minutes higher (95% CI, 2.5–7.7 minutes higher). The quality of evidence was high (see **Figure S23**).

Two observational studies assessed the effects of sodium oxybate on the ability to maintain wakefulness in patients with NT1 using the MWT.[82,83] The mean MWT score pre-/post difference ranged from 6.1–11.9 minutes higher in these patients. The quality of evidence was very low due to imprecision (see **Table S39**).

Cataplexy: Two RCTs[74,75] evaluated the decrease in weekly cataplexy episodes in patients with NT1. Both studies demonstrated a cataplexy reduction of 9%. This reduction was clinically insignificant. The quality of evidence was high (see **Table S40**).

An observational study[78] also evaluated weekly cataplexy episodes and reported a pre-/post percentage difference in cataplexy reduction of 86.4% in patients with NT1. This demonstrates a clinically significant reduction. The quality of evidence was very low due to imprecision (see **Table S41**).

One RCT[84] evaluated the change in weekly cataplexy episodes 2 weeks after the withdrawal of sodium oxybate in patients with NT1. Patients recorded the incidence of weekly cataplexy attacks in daily diaries. The study demonstrated a clinically significant 164.4% increase in weekly cataplexy rate following the abrupt cessation of sodium oxybate therapy in these patients when compared with those who continued sodium oxybate. This increase was clinically significant. The quality of evidence was moderate due to imprecision (see **Table S42**).

Disease severity: One RCT reported an improvement in 58% of patients with NT1 on sodium oxybate, which is a clinically significant change.[75] The quality of evidence was high (see **Table S43**).

Another RCT reported an improvement in 48% of adult patients with unspecified narcolepsy, which is a clinically significant change.[44] The quality of evidence was high (see **Table S44**).

Quality of life: One RCT[77] evaluated the effect of sodium oxybate in patients with NT1 utilizing the physical health summary score of the SF-36. The mean change from baseline in patients on sodium oxybate was an estimated 1.8 points higher (95% CI, 0.0–3.7 points higher) compared to placebo, which was not clinically significant. The quality of evidence was moderate due to imprecision (see **Table S45**).

The above RCT[77] also evaluated the effect of sodium oxybate in patients with NT1 utilizing the mental health summary score of the SF-36. The mean change from baseline in patients on sodium oxybate was an estimated 1.7 points higher (95% CI, 1.6 points lower–5.0 points higher) compared to placebo. This was not a clinically significant change. The quality of evidence was moderate due to imprecision (see **Table S46**).

One RCT[85] evaluated the effect of sodium oxybate in patients with NT1 utilizing the Functional Outcomes of Sleep Questionnaire (FOSQ) score. Data reported were not suitable for analysis.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality.

Fatigue: One RCT with patients with NT1 evaluated fatigue by using the SF-36 energy and vitality component score.[77] The mean SF-36 vitality domain score pre-/post difference in patients with NT1 was an estimated 4.9 points higher (95% CI, 2.4–7.4 points higher) when compared to placebo. This was a clinically significant change. The quality of evidence was moderate due to imprecision (see **Table S47**).

Sleep quality: Two RCTs[53,86] reported on sleep quality in posthoc analyses of responses to a single question on the Pittsburgh Sleep Quality Index (PSQI), which asks, "During the past month, how would you rate your sleep quality overall?" with responses of 0 denoting "very good" to 3 denoting "very bad." Both publications presented data that were not sufficient to evaluate the clinical significance of the findings. Quality of evidence could not be assessed.

Overall quality of evidence

The TF determined that the overall quality of evidence for sodium oxybate to treat narcolepsy compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness, cataplexy, and disease severity.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects favored sodium oxybate. Overall, the desirable critical outcomes are moderate. The TF acknowledged that the full benefits of sodium oxybate typically manifest weeks to months after goal titration and the assessment period of clinical studies may be shorter, thereby underestimating full efficacy.

In patients with narcolepsy, the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances (including obstructive sleep apnea) was 0.10 (95% CI, 0.05–0.14), of nausea was 0.10 (95% CI, 0.00–0.21), of urinary/renal disturbances (including nocturnal enuresis) was 0.06 (95% CI, 0.01–0.11), of diarrhea was 0.04 (95% CI, –0.02 to 0.09), and of chest discomfort was 0.02 (95% CI, 0.0–0.04)[76,78,85] (see **Figures S79–S86** in the supplemental material). Common adverse events in the observational studies included sleep disturbances, headache, nausea, muscle pain, and weight loss.

Across all RCTs reporting on the use of sodium oxybate, the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances was 0.10 (95% CI, 0.05–0.14), of nausea: 0.10 (95% CI, 0.00–0.21), of dizziness: 0.9 (95% CI, 0.04–0.14), of urinary/renal disturbances: 0.07 (95% CI, 0.22–0.11), of headache: 0.04 (95% CI, –0.17 to 0.08) diarrhea: 0.04 (95% CI, –0.01 to 0.10), chest discomfort: 0.02 (95% CI, 0.0–0.04), and anxiety or nervousness: 0.01 (95% CI, –0.05 to 0.07)[76,78,85,87] (see **Figures S79–S86**). Commonly reported adverse events reported across all observational studies on the use of sodium oxybate included sleep disturbances (22.7%), nausea (20.4%), headache (17.25%), dizziness (17.08%), and confusion (12.8%).[75,79,81,83]

Finally, sodium oxybate 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. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.[88]

Resource use

At the time of this publication, the NADAC did not report on this drug's pricing. Cost-effectiveness has not been systematically evaluated in the United States. In Denmark, the cost-effectiveness of sodium oxybate therapy in narcolepsy was compared to that of a common combination of methylphenidate and venlafaxine—the former was more expensive, with an annual estimated cost of Swedish Krona (SEK) 82,927 vs SEK 18,301.[89] Because of the risk of CNS depression, as well as abuse and misuse, sodium oxybate is only available through risk evaluation mitigation strategy (REMS) programs. This drug is only available at certified specialty pharmacies and not in retail pharmacies. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients with narcolepsy would likely use sodium oxybate when compared to no treatment. This assessment reflects the TF's clinical judgment, based on sodium oxybate's efficacy to reduce cataplexy,

increase quality of life, and decrease daytime sleepiness and disease severity. The TF determined that patients would likely accept a small risk of AEs for this benefit but acknowledged that some patients find twice-per-night dosing to be inconvenient. A balanced discussion between patients and their clinical provider about the consequences of untreated narcolepsy will be beneficial.

Solriamfetol

The TF literature identified 4 randomized, double-blind placebo-controlled trials of solriamfetol conducted with patients with unspecified narcolepsy.[90–93] Endpoints for all RCTs were excessive daytime sleepiness as measured by the ESS and MWT and disease severity using the clinical global impression scores of change (CGI-C). One study included 18 patients with NT1 and 15 patients with NT2 and used a crossover design of solriamfetol 300 mg goal dose vs placebo with endpoints measured 2 weeks after treatment initiation.[91] Another study was a phase 2b parallel-group trial conducted at 28 centers in the United States comparing solriamfetol doses 150–300 mg to placebo among a total of 93 participants. More patients in this study had NT2 (n = 60) than NT1 (n = 33) and the majority were female (64.5%). Endpoints were assessed at 4 weeks (solriamfetol 150 mg vs placebo) and 12 weeks (solriamfetol 300 mg vs placebo).[92] Notably, both studies had inclusion criteria requiring participants to have baseline ESS scores ≥ 10 and baseline MWT sleep latencies ≤ 10 minutes. Another study was a phase 3 study, performed at 50 study centers in the United States and Canada and 9 centers in Finland, France, Germany, and Italy. This was the Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness (TONES) 2 study from the TONES Phase 3 program.[93] One study was a randomized, double-blind, placebo-controlled, multicenter, 4-arm parallel-group study, wherein quality-of-life endpoints were assessed at 12 weeks.[90] Notably, the pooled analyses were conducted using data on 75 mg, 150 mg, and 300 mg doses, but the FDA has only approved the use of solriamfetol at 75 mg and 150 mg for patients with narcolepsy.[94]

The meta-analyses and figures and tables are in **Figures S24–S27** and **Tables S49–S51** in the supplemental material. A summary of findings table is provided in **Table S52** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for cataplexy, accident risk, and work/school performance.

Excessive daytime sleepiness: Two RCTs evaluated the effect of solriamfetol on excessive daytime sleepiness using the ESS[91,93] and showed a clinically significant difference of 3.8 points lower (95% CI, 2.5–to 5.1 points lower) on solriamfetol compared to placebo. The quality of evidence was high (see **Figure S24**).

In the parallel-design RCT,[92] participants taking solriamfetol reported an estimated mean ESS difference of 6.2 points lower (95% CI, 4.0–8.4 points lower) than that reported in the placebo group. This was a clinically significant reduction. The quality of evidence was moderate due to imprecision (see **Table S49**).

The above 3 RCTs evaluated the effect of solriamfetol on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT.[91–93] The meta-analysis demonstrated that solriamfetol met the clinical significance threshold on the MWT with a mean difference of 9.5 minutes higher (95% CI, 6.3–12.7 minutes higher) when compared to placebo. The quality of evidence was high (see **Figure S25**).

Disease severity: Three studies reported on the percentage of patients with unspecified narcolepsy reporting overall improvement in Clinical Global Impression of Change (CGI-C) scores.[91–93] The improvement in the scores in the solriamfetol group ranged from 36.4%–47.7% when compared to the placebo group.[91–93] This met the clinical significance threshold. The quality of evidence was high (see **Table S50**).

Two RCTs also reported on the percentage of patients with unspecified narcolepsy reporting overall improvement in Patient Global Impression of Change (PGI-C) scores.[92,93] PGI-C in the solriamfetol group was clinically significant and ranged from 37.2%–54.7% when compared to placebo. The quality of evidence was high (see Table S51).

Quality of life: One RCT[90] evaluated the effect of solriamfetol on quality of life in patients with unspecified narcolepsy utilizing the FOSQ (short version) score. The mean change from baseline in patients on solriamfetol was 1.1 points higher (95% CI, 0.2–2.0 points higher) compared to placebo, which was clinically significant. The quality of evidence was moderate due to imprecision (see **Figure S26**).

The above study[90] also analyzed quality of life with the physical health summary component of the SF-36. The mean change from baseline in patients on solriamfetol was 1.7 points higher (95% CI, 0.1 points lower–3.5 points higher) compared to placebo, which did not meet the threshold for clinical significance. The quality of evidence was moderate due to imprecision (see **Figure S27**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data on fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for solriamfetol for the treatment of narcolepsy compared to placebo was considered high based on the critical outcomes reported in the literature. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness, disease severity, and quality of life.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is in favor of solriamfetol.

In patients with narcolepsy, the risk difference between placebo in the use of solriamfetol in the RCTs were as follows: headache: 0.12 (95% CI, –0.18 to 0.06), decreased appetite: 0.12 (95% CI, 0.07–0.17), and insomnia: 0.09 (95% CI, –0.04 to 0.21)[91–93] (see **Figures S87–S89** in the supplemental material). Most AEs were mild or moderate in severity. Other side effects including chest discomfort, anxiety, and muscle tightness ranged in frequency from 6.1%–9.1% in the solriamfetol treatment group.[91–93] One study reported 2 serious AEs in the solriamfetol treatment group (conversion disorder and acute cholecystitis) not believed to be related to study medication.[92]

No other studies included in the systematic review reported on the use of solriamfetol (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

Solriamfetol 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.[95]

Resource use

At the time of this publication, there is no drug cost mentioned in the NADAC. As with other interventions, it is speculated that costs are likely to vary because of factors including insurance coverage, copays, and deductibles. No included studies assessed the cost-effectiveness of solriamfetol.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and that the majority of patients with narcolepsy would probably use solriamfetol to treat excessive daytime sleepiness when compared to no treatment given its large favorable effects (objective and subjective) and mostly mild to moderate side effects.

Triazolam

The TF's review of the literature identified 1 single-blind within-subject crossover study of triazolam (0.25 mg) in 10 patients with NT1.[96]

The figures are provided in **Figures S28–S30** in the supplemental material. A summary of findings table is provided in **Table S53** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. The study identified in our literature review did not report data for cataplexy, disease severity, quality of life, accident risk, and work/school performance.

Excessive daytime sleepiness: One RCT[96] evaluated the effect of triazolam on the ability to maintain wakefulness in patients with NT1 using the MWT. The mean MWT score in the triazolam group was 0.3 minutes higher (95% CI, 2.9 minutes lower–3.5 minutes higher) compared to placebo. This was not clinically significant (see **Figure S28**).

The same study also assessed the effects of triazolam on excessive daytime sleepiness using the MSLT. The mean MSLT score in the triazolam group was 0.2 minutes lower (95% CI, 0.4 minutes lower–0.9 minutes higher) compared to placebo. This was also not clinically significant (see **Figure S29**). The quality of evidence for both these findings was downgraded to moderate due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. The study identified in our literature review did not report data for fatigue.

Sleep quality: One RCT[96] evaluated sleep quality on the basis of sleep efficiency. The mean difference in sleep efficiency in the triazolam group was 9.9% (95% CI, 3.0%–16.8% higher) when compared to placebo. This was not clinically significant. Quality of evidence was moderate due to imprecision (see Figure S30).

Overall quality of evidence

The TF determined that the overall quality of evidence for the treatment of narcolepsy with triazolam was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects is inconclusive. The use of triazolam for narcolepsy showed some modest improvements in sleep quality and objective sleepiness, but none met clinical significance thresholds. Side effects were not mentioned in the manuscript. The balance of risks and harms is likely different for pregnant and breastfeeding women.

No other studies included in the systematic review reported on the use of triazolam (irrespective of the indication). Labeling states that triazolam is contraindicated in pregnant women.

Resource use

At the time of this publication, per the National Average Drug Acquisition Cost (NADAC) database, the unit cost of 0.125–0.25 mg tablets ranged from $1.78–$1.48. Resource use otherwise should not be high compared to other medications to treat narcolepsy. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was possibly important uncertainty regarding whether the majority of patients with narcolepsy

would use triazolam to treat their disease. The important outcome measure of sleep quality neared but did not reach the clinical threshold, and adverse effects were not specified in the study.

TREATMENT OF IDIOPATHIC HYPERSOMNIA

The aims of the current literature review and data analyses were focused on addressing the treatment of idiopathic hypersomnia. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, resource use, and patient values and preferences that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. The interventions below are listed in alphabetical order.

Clarithromycin

The TF identified 1 RCT that examined the effects of clarithromycin on 20 adult patients with central disorders of hypersomnolence, including 10 patients with idiopathic hypersomnia.[97] The dose of clarithromycin was 1,000 mg/day, divided into 2 doses, compared to placebo in a 5-week crossover study.

The literature review also identified 1 retrospective observational study of clarithromycin for hypersomnolence disorders.[98] This study included 24 adult patients with idiopathic hypersomnia and one 17-year-old patient. Clarithromycin doses varied between 1000 and 2000 mg per day, divided into 2 doses. Data for outcomes of these 2 studies specific to participants with idiopathic hypersomnia were obtained from personal communication via email with the corresponding author in November 2018. Details of data obtained from this communication have been indicated in the supplemental material.

The figures and tables are provided in **Figures S31–S36** and **Table S54** in the supplemental material. A summary of findings table is provided in **Table S55** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. None of the studies identified in our literature review reported data for work/school performance.

Excessive daytime sleepiness: One RCT evaluated the effect of clarithromycin on excessive daytime sleepiness in patients with idiopathic hypersomnia using the ESS.[97] This study showed a clinically significant mean reduction of 3.3 points lower on the ESS (95% CI, 7.6 points lower–1.0 points higher) with patients taking clarithromycin than the placebo group. The quality of evidence was moderate due to imprecision (see **Figure S31**).

One RCT evaluated the effect of clarithromycin on excessive daytime sleepiness in patients with idiopathic hypersomnia using the SSS.97 Considering only the patients with idiopathic hypersomnia, this study showed a clinically insignificant difference of 0.8 points lower (95% CI, 2.2 points lower–0.6 points higher) with patients taking clarithromycin than the placebo group. The quality of evidence was moderate due to imprecision (see **Figure S32**).

Disease severity: One observational study measured change in disease severity with clarithromycin using a scale of improved, ineffective, or stopped due to side effects.[98] Seventy-one percent of patients with idiopathic hypersomnia were rated as improved with clarithromycin, 21% found it to be ineffective, and 8% stopped treatment due to side effects. This was a clinically significant outcome in favor of clarithromycin. The quality of evidence was downgraded to very low due to imprecision (see **Table S54**).

Quality of life: One RCT evaluated the effect of clarithromycin on quality of life in patients with idiopathic hypersomnia using 2 different tools, the SF-36 and the Functional Outcomes of Sleep Questionnaire (FOSQ).[97] Total SF-36 scores, calculated as an average of all subscores, had a clinically significant mean difference of 9.7 points higher (95% CI, 1.6 points lower–21.0 points higher) with clarithromycin vs placebo (see **Figure S33**).

FOSQ scores showed a clinically significant difference of 1.9 points higher (95% CI, 0.5 points lower–4.3 points higher) with clarithromycin vs placebo.[97] The quality of evidence was moderate due to imprecision (see **Figure S34**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. None of the studies identified in our literature review reported data for sleep inertia.

Cognitive performance

One RCT measured the effects of clarithromycin on vigilance in patients with idiopathic hypersomnia using the psychomotor vigilance task (PVT).97 The measure reciprocal of the reaction time (RRT) was collected from the 10-minute PVT for assessment of cognitive performance.

The mean improvement in RRT with clarithromycin over placebo was 0.3 millisec^{-1} (95% CI, 0.4 points lower–1.1 points higher). This represents a clinically significant improvement of 10.5% in patients on clarithromycin when compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S35**).

Fatigue: One RCT measured the effects of clarithromycin on fatigue in patients with idiopathic hypersomnia using the SF-36 energy and vitality subscale.[97] There was a clinically significant improvement of 14.1 points higher vitality (95% CI, 7.9 points lower–36.1 points higher) with clarithromycin than with placebo. Quality of evidence was low due to serious imprecision (see **Figure S36**).

Overall quality of evidence

The TF concluded that the overall quality of evidence for clarithromycin for the treatment of idiopathic hypersomnia compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness, disease severity, and quality of life.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is likely in favor of clarithromycin. Use of clarithromycin resulted in improvements in the critical outcomes of daytime sleepiness, quality of life, and disease severity when compared to placebo. The TF judged the undesirable effects to be moderate.

One RCT reported adverse events when clarithromycin was used in the treatment of central disorders of hypersomnolence, including idiopathic hypersomnia.[97] The number of participants experiencing at least 1 adverse event was no different between clarithromycin and placebo treatment periods. Commonly reported adverse events included gastrointestinal symptoms of any kind (73%), dysgeusia or dysosmia (68%), nausea (32%), insomnia (27%), and diarrhea (18%). In an observational study of clarithromycin for treatment of hypersomnolence disorders including idiopathic hypersomnia,[98] commonly reported adverse events reported included gastrointestinal symptoms (9%), bad taste (4%), worsened sleep quality (2%), headache (2%), and weakness (2%). Four percent of participants discontinued clarithromycin because of dysgeusia.

No other studies included in the systematic review reported on the use of clarithromycin (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

Although clarithromycin does not have any black box warnings, the FDA recently released an alert advising caution when using clarithromycin in people 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.[99] Based on animal data, clarithromycin may cause fetal harm. Labeling states that clarithromycin should not be used by pregnant women. 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.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 500 mg dose was $0.58/tablet and $4.04 per unit for the extended-release (ER) tablet of the same dose.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles. No included studies assessed the cost-effectiveness of clarithromycin.

Patient values and preferences

The TF determined there was probably no uncertainty or variability in how much people value the main study outcomes and that the majority of patients would likely use clarithromycin when compared to no treatment for their idiopathic hypersomnia. This assessment reflects the TF's clinical judgment, based on clarithromycin's efficacy in reducing daytime sleepiness and improving quality of life, relative to its moderately severe side effect profile.

Flumazenil

The TF literature search identified 1 retrospective chart review of flumazenil for treatment of central disorders of hypersomnolence, which included 36 patients with idiopathic hypersomnia.[100] In addition to having a diagnosis of idiopathic hypersomnia, participants had to have symptoms that were refractory to multiple conventional wake-promoting medications because of lack of effect, intolerable side effects, or both. Flumazenil was compounded into sublingual and transdermal forms, used together or individually. Sublingual flumazenil doses ranged from 24 mg/day–60 mg/day, divided into 4 doses/day. Transdermal doses ranged from 12 mg/day–48 mg/day, divided into up to 4 doses/day. Data for outcomes of this study specific to participants with idiopathic hypersomnia were obtained from personal communication via email with the corresponding author in June 2019. Details of data obtained from this communication have been indicated in the supplemental material.

The data table is provided in **Table S56** in the supplemental material. A summary of findings table is provided in **Table S57** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The study identified in our literature review did not report on a sufficient number of patients for the outcome tools of interest.

Disease severity: One observational study assessed the effects of flumazenil on overall disease severity of idiopathic hypersomnia by using a dichotomous measure of symptomatic benefit/no symptomatic benefit.[100] Sixty-four percent of the patients with idiopathic hypersomnia were judged to have symptomatic benefit from flumazenil. This was considered clinically significant. Quality was downgraded to very low due to imprecision (see **Table S56**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. The study identified in our literature review did not report data for cognitive performance, fatigue, or sleep inertia.

Overall quality of evidence

The TF determined that the overall quality of evidence for flumazenil to treat idiopathic hypersomnia was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of disease severity.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects is inconclusive.

One observational study reported on adverse events occurring during flumazenil treatment for idiopathic hypersomnia and other central disorders of hypersomnolence.[100] Two serious adverse events—a transient ischemic attack and an asymptomatic, radiographically identified central nervous system vasculopathy—were observed in patients with risk factors for these vascular events. The most common adverse events with flumazenil were dizziness (13%), worsening of sleepiness that was usually transient (12%), headache (7%), anxiety (7%), and other mood disturbances (6%).

No other studies included in the systematic review reported on the use of flumazenil (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

The black box warning states that this drug has been associated with seizures. Based on animal data, flumazenil may cause fetal harm. Human data are insufficient to determine risk. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[101]

Resource use

The NADAC database has listed the unit price for 0.1–0.5 mg/5 mL vials as $1.26.[26] There is no cost listed for lozenges or transdermal cream. Because flumazenil is currently approved in liquid form for IV use, it must be formulated by specialized compounding pharmacies into a transdermal cream or sublingual lozenge—for topical or mucosal absorption, respectively. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles. Accessibility is also a variable factor considering that specialized pharmacies are required to formulate the drug. No included studies assessed the cost-effectiveness of flumazenil.

Patient values and preferences

The TF determined that there was possibly important uncertainty regarding whether or not the majority of patients with narcolepsy would use flumazenil to treat their disease. The intervention demonstrated symptomatic relief but also serious adverse events.

Methylphenidate

Our literature search identified 1 retrospective, observational study of methylphenidate in 61 patients with idiopathic hypersomnia.[102] This was a retrospective review of charts of eligible patients where response to treatment was graded utilizing an internally developed scale. The median duration of the follow-up period was 2.4 (± 4.7) years, and the median number of patient visits was 6 (± 3). The mean total daily dose was 50.9 (± 27.3) mg.

The data table is provided in **Table S58** in the supplemental material. A summary of findings table is provided in **Table S59** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for excessive daytime sleepiness, quality of life, or work/school performance.

Disease severity: The observational study[102] reported a change in the disease severity of idiopathic hypersomnia with methylphenidate using a scale of complete response, partial response, and poor response. Of the 61 patients treated with methylphenidate, 25 (41%) were judged to have complete response, 13 (21%) were judged to have partial response, and 2 (3%) were judged to have poor response or were changed to a treatment other than or in addition to methylphenidate. This is clinically significant. The quality of evidence was very low because of imprecision (see **Table S58**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. The study identified in our literature review did not report data for cognitive performance, fatigue, or sleep inertia.

Overall quality of evidence

The TF determined that the overall quality of evidence for methylphenidate to treat idiopathic hypersomnia was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of disease severity.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is likely in favor of methylphenidate.

In patients with idiopathic hypersomnia, the most common reported adverse events that limited dose escalation or resulted in methylphenidate discontinuation were nervousness (approximately 25%), palpitations (approximately 15%), and insomnia (approximately 10%).[102]

Across all RCTs included in the systematic review that reported on the use of methylphenidate (irrespective of the indication), most adverse events were mild and included loss of appetite (20%), nausea (10%), vomiting (10%), and palpitations (10%).[35] Commonly reported adverse events reported across all observational studies on the use of methylphenidate included dry mouth (38.6%), sweating (34.9%), headache (24.5%), stomach discomfort (21.6%), and loss of appetite (16.9%).[34] The balance of risks and harms is likely different for pregnant and breastfeeding women.

In addition, this drug 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. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Based on animal data, methylphenidate may cause fetal harm. Human data are insufficient to determine risk.[36]

Resource use

At the time of this publication, the NADAC reported the drug's pricing ranged from $0.14/mL for solution, $0.12–$2.50/tablet (5–20 mg), and $1.95–$3.51/capsule (10–60 mg).[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF concluded that there was probably no important uncertainty or variability in how people value the critical outcome, and that the majority of patients would probably use methylphenidate when compared to no treatment for their idiopathic hypersomnia. Disease severity is likely important to patients.

Modafinil

The TF review of the literature identified 1 RCT that examined the effects of modafinil vs placebo on 31 adult patients with idiopathic hypersomnia.[62] This was a parallel-group study of modafinil 200 mg/day, divided into 2 doses. Data for the outcomes of this study were obtained from personal communication via email with the corresponding author in November 2018. Details of data obtained from this communication have been indicated in the supplemental material.

TF literature review also identified 4 observational studies of the effect of modafinil in adult patients with idiopathic hypersomnia.[39,102–104] Three of these studies were retrospective, based on chart review and/or clinical interview.[39,102,103] Sample sizes in these observational studies ranged from 25–104. One observational study involved a prospective cohort with 18 patients diagnosed with idiopathic hypersomnia on modafinil.[104] Modafinil doses varied between 100 and 600 mg per day.

The TF did not identify any RCTs or observational studies evaluating modafinil use in children with idiopathic hypersomnia, although the observational study included 3 adolescents aged 16.6 years and older.[39]

The meta-analyses, figures, and tables are provided in **Figures S37–S39** and **Tables S60–S62** in the supplemental material. A summary of findings table is provided in **Table S63** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. None of the studies identified in our literature review reported data for quality of life or work/school performance.

Excessive daytime sleepiness: One RCT evaluated the effect of modafinil on excessive daytime sleepiness using the ESS.[62] This study showed a clinically significant difference of 4.0 points lower ESS in the modafinil group (95% CI, 7.3 points –0.7 points lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S37**).

Two observational studies[39,103] used the ESS and showed clinically significant pre-/post improvements in the ESS ranging from reductions of 3.0–6.0 points, supporting the finding of the RCT. The quality of evidence was low (see **Table S60**).

One RCT evaluated the effect of modafinil on the ability to maintain wakefulness using the MWT.[62] This RCT showed a clinically significant difference of 3.0 minutes longer wakefulness in the modafinil group (95% CI, 5.8 minutes shorter–11.8 minutes longer) when compared to placebo. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S38**).

Disease severity: One RCT evaluated disease severity, using the Clinical Global Impression (CGI) rating scale.[62] This study found a clinically significant decrease in CGI severity of 1.0 point (95% CI, 0.1–1.9 points lower) with modafinil when compared with placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S39**).

Two observational studies used study-specific scales to measure change in disease severity with modafinil treatment.[102,104] One observational study (n = 18) reported change in disease severity using a scale of "improved," "ineffective," "stopped for side effects," or "not followed up."[104] Eighty-three percent of the patients reported an improvement with modafinil (see **Table S61**).

The other observational study recorded change in disease severity in 85 patients, of whom 50 were prescribed modafinil using a scale of complete (excellent or satisfactory) response, partial (doing better, improved) response, and poor (still sleepy, changed to another medication).[102] Per the last recorded follow-up visit, only 25 patients remained on modafinil. Of the 50 patients who started treatment with modafinil, 18 (36%) reported complete symptomatic relief, 4 (8%) reported partial symptomatic relief, and 3 (6%) reported no benefit (see **Table S62**). The quality of evidence was considered very low due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. None of the studies identified in our literature review reported data for cognitive performance, fatigue, or sleep inertia.

Overall quality of evidence

The TF determined that the overall quality of evidence for modafinil for the treatment of idiopathic hypersomnia compared to placebo was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness and disease severity.

Benefits and harms

The TF judged that the balance between desirable and undesirable effects favors the use of modafinil. The use of modafinil demonstrated reductions in daytime sleepiness and improvements in disease severity when compared to placebo and in observational studies.

In general, the adverse effects of modafinil reported by people with idiopathic hypersomnia seemed comparable to those reported when it was used for other hypersomnolence disorders. One RCT reported the frequency of adverse events with modafinil in adult patients with idiopathic hypersomnia.[62] The proportion of patients with any adverse events on modafinil was not significantly different than those on placebo (53% with modafinil and 64% with placebo). However, specific adverse events were more common in the modafinil-treated group, including headaches (26%) and gastrointestinal symptoms (20%). Observational studies of modafinil for idiopathic hypersomnia have reported similar rates of headache of 9% to approximately 23%, rates of nausea of 4%–13%, and rates of combined gastrointestinal symptoms of 9 to approximately 15%.[39,102,103]

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk differences of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth: –0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06)[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[105] 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.25 Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 100–200 mg modafinil doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles. No included studies assessed the cost-effectiveness of modafinil.

Patient values and preferences

The TF judged that the majority of individuals with idiopathic hypersomnia would likely choose to use modafinil rather than no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's efficacy in reducing daytime sleepiness and its relatively benign side effect profile.

Pitolisant

The TF identified 1 retrospective, observational study of pitolisant for nonnarcoleptic central hypersomnia.[69] This study included 65 patients with idiopathic hypersomnia. In addition to having a diagnosis of idiopathic hypersomnia, participants had to have symptoms that were refractory to multiple conventional wake-promoting medications. Pitolisant doses varied between 5 mg/day and 50 mg/day, dosed once per day in the morning.

The data table is provided in **Table S64** in the supplemental material. A summary of findings table is provided in **Table S65** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for disease severity, quality of life, or work/school performance.

Excessive daytime sleepiness: One observational study evaluated the effect of pitolisant on excessive daytime sleepiness in idiopathic hypersomnia, using the ESS.[69] Pitolisant resulted in a clinically significant reduction in ESS of 2.7 points (95% CI, 1.6–3.7 points lower). Quality of evidence was downgraded to very low due to imprecision (see **Table S64**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. The study identified in our literature review did not report data for cognitive performance, fatigue, or sleep inertia.

Overall quality of evidence

The TF determined that the overall quality of evidence for the use of pitolisant in idiopathic hypersomnia was very low based on the critical outcome reported in the literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF judged that the balance between desirable and undesirable effects probably favors the use of pitolisant. Use of pitolisant resulted in a clinically significant improvement in daytime sleepiness based on the observational study.

In patients with idiopathic hypersomnia, there were insufficient data to conduct a meta-analysis of pitolisant side effects. Based on a single observational study, the most common adverse events with pitolisant were gastrointestinal pain (15.4%), increased appetite and weight gain (14.1%), headache (12.8%), insomnia (11.5%), and anxiety (9%).[69] Two patients developed depressive symptoms, 1 with suicidal ideation, which resolved after discontinuation of pitolisant. Therefore, the TF judged the undesirable effects to be moderate.

In patients with narcolepsy, the risk difference of the commonly reported adverse effects between pitolisant and placebo were as follows: nausea: 4.9 (95% CI, 0.98–24.12), headache: 0.12 (95% CI, –0.05 to 0.28), and insomnia: 0.09 (95% CI, 0.01–0.18). None of them resulted in treatment cessation. Four AEs were considered severe: abdominal discomfort, nausea, malaise, and insomnia[41,67,68] (see Figures S76–S78). The balance of risks and harms is likely different for pregnant and breastfeeding women.

Pitolisant has low abuse potential and thus is not a scheduled federally controlled substance. Based on animal data, pitolisant may cause fetal harm. Human data are insufficient to determine risk. 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.[70]

Resource use

As pitolisant was recently approved by the FDA, there are no available cost data in the NADAC database. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles. No included studies assessed the cost-effectiveness of pitolisant.

Patient values and preferences

The TF judged that some patients with idiopathic hypersomnia would likely use pitolisant when compared to no treatment. This assessment reflects the TF's clinical judgment, based on pitolisant's reductions in daytime sleepiness, relative to its moderately severe side effect profile.

Sodium oxybate

The TF identified 1 retrospective, observational study assessing the effects of sodium oxybate on excessive daytime sleepiness measured by the ESS in 46 adults with idiopathic hypersomnia.[81] The average dose of sodium oxybate at the end of titration was 4.3 g, with 66% of patients taking a single nocturnal dose rather than twice-nightly dosing.

The data table is provided in **Table S66** in the supplemental material. A summary of findings table is provided in **Table S67** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: One off-label, retrospective observational study evaluated the effect of sodium oxybate on excessive daytime sleepiness in idiopathic hypersomnia, using the ESS.[81] Sodium oxybate resulted in a clinically significant reduction of ESS scores of 2.7 points lower (95% CI, 5.0 points lower–0.4 points higher). Quality of evidence was very low due to imprecision (see **Table S66**).

Disease severity: The observational study evaluated the effect of sodium oxybate on overall disease severity in patients with idiopathic hypersomnia, using a 4-point scale assessing the global benefit.[81] This ranged from 0, indicative of a complete lack of benefit, to 3, indicative of major benefit. This was completed by the patients and by their neurologists. Average global benefit as reported by patients was 1.6, as was the average global benefit rated by neurologists. Data reported were not suitable for analysis.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: cognitive performance, fatigue, and sleep inertia. The study identified in our literature review did not report data for cognitive performance or fatigue.

Sleep inertia: The observational study[81] evaluated the effect of sodium oxybate on sleep inertia in patients with idiopathic hypersomnia and reported a benefit on severe sleep inertia in 71% (24/34) of patients. Data reported were not suitable for analysis.

Overall quality of evidence

The TF determined that the overall quality of evidence for the use of sodium oxybate in idiopathic hypersomnia was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF judged that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate for patients with idiopathic hypersomnia. Use of sodium oxybate resulted in improvements in daytime sleepiness and sleep inertia.

In people with idiopathic hypersomnia, the most common side effects reported in a single observational study were nausea (40%) and dizziness (34%). Other events included headache (approximately 29%), vomiting (approximately 14%), and sedation (approximately 12%).[81]

Across all RCTs reporting on the use of sodium oxybate, the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances was 0.10 (95% CI, 0.05–0.14), of nausea: 0.10 (95% CI, 0.00–0.21), of dizziness: 0.9 (95% CI, 0.04–0.14), of urinary/renal disturbances: 0.07 (95% CI, 0.22–0.11), of headache: 0.04 (95% CI, –0.17 to 0.08) diarrhea: 0.04 (95% CI, –0.01 to 0.10), chest discomfort 0.02 (95% CI, 0.0–0.04), and anxiety or nervousness: 0.01(95% CI,

–0.05 to 0.07)[76,78,85,87] (see **Figures S79–S86**). Commonly reported adverse events reported across all observational studies on the use of sodium oxybate included sleep disturbances (22.7%), nausea (20.4%), headache (17.25%), dizziness (17.08%), and confusion (12.8%).[75,79,81,83]

Finally, sodium oxybate 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. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.[88]

Resource use

At the time of this publication, the NADAC did not report on this drug's pricing. Because of the risk of CNS depression, and abuse and misuse, sodium oxybate is only available through REMS programs. This drug is only available at certified specialty pharmacies and not in retail pharmacies. According to the price guide on https://www.drugs.com, the cost for cash-paying patients of sodium oxybate oral liquid (500 mg/mL) is around $4,829 for a supply of 180 mL, depending on the pharmacy. Prices are for cash-paying customers only and are not valid with most insurance plans. Costs are likely to vary because of factors including, but not limited to, insurance providers, variations in market prices, and variability in prescriptions. No included studies assessed the cost-effectiveness of sodium oxybate.

Patient values and preferences

The TF judged that some patients would likely use sodium oxybate when compared to no treatment. This assessment reflects the TF's clinical judgment, based on sodium oxybate's reductions in daytime sleepiness and sleep inertia, relative to its moderately severe side effect profile.

TREATMENT OF KLEINE-LEVIN SYNDROME

The aims of the current literature review and data analyses were focused on addressing the treatment of Kleine-Levin syndrome. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, resource use, and patient values and preferences that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. The interventions below are listed in alphabetical order.

Lithium

The TF identified 1 prospective, open-label, single-center study that included 71 patients with Kleine-Levin syndrome (children: n = 40).[106] In this study, the median dose of lithium carbonate taken by patients was 1,000 mg/day and patients were followed for a mean period of 21.5 ± 17.8 months.

The data tables are provided in **Tables S68–S70** in the supplemental material. A summary of findings table is provided in **Table S71** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Disease severity: In the above study,[106] disease severity was measured by the change in total number of episodes within the observational period, the change in episode frequency per year, and mean episode duration. The total number of episodes decreased by 10.5 episodes (95% CI, 13.3–7.7 episodes lower). The number of episodes decreased by 79.5%, which was clinically significant (see **Table S68**).

The frequency of Kleine-Levin syndrome bouts decreased by 2.5 episodes per year (95% CI, 3.3–1.7 episodes lower) post-lithium use compared to prelithium use. The mean episode frequency pre-/post difference was 65.8%, which was clinically significant (see **Table S69**).

The mean episode duration also decreased by 7.3 days (95% CI, 12.1–2.6 days lower). The mean episode duration pre-/post difference was 42.2%, which was clinically significant (see **Table S70**).

The quality of evidence for each of these measures was rated as very low due to imprecision.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and mood. The study identified in our literature review did not report data for fatigue or mood.

Overall quality of evidence

The TF determined that the quality of evidence for lithium therapy for Kleine-Levin syndrome was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcome of disease severity.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is most likely in favor of lithium.

There were no serious adverse events reported in the open-label study of lithium in patients with Kleine-Levin syndrome, though 5 patients discontinued treatment because of side effects. Almost 50% of the patients treated with lithium for

Kleine-Levin syndrome experienced at least 1 adverse event with most common side effects being tremor (approximately 38%), polyuria-polydipsia (approximately 22%), diarrhea (approximately 14%), and subclinical hypothyroidism (11.3%). There was no report of lithium toxicity (listed as black box warning) in this study.[106]

No other studies included in the systematic review reported on the use of lithium (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

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. Based on animal studies, lithium may cause fetal harm. Human studies suggest fetal harm but are insufficient to determine risk.[107]

Resource use

This medication is available in the form of capsules and extended-release (ER) tablets. At the time of this publication, the NADAC reported the pricing of lithium carbonate ranging from $0.07 per unit of 150 mg capsules to $0.15 per unit of 600 mg capsules. The ER tablet pricing raged from $0.15 per unit for 300 mg to $0.19 per unit for 450 mg.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was no important uncertainty or variability in patient values or preferences for shorter Kleine-Levin syndrome symptomatic bouts or reduced frequency of Kleine-Levin syndrome symptomatic episodes. The TF noted large desirable anticipated effects and moderate undesirable effects for use of lithium therapy in Kleine-Levin syndrome. Overall, the TF felt that patients with Kleine-Levin syndrome may favor lithium use over no treatment.

Methylprednisolone

The TF identified 1 observational, open-label study of intravenous (IV) methylprednisolone during prolonged episodes of Kleine-Levin syndrome bouts vs abstention.[108] The study included 26 patients with Kleine-Levin syndrome who received 1 g/day IV methylprednisolone for 3 days during 1–6 Kleine-Levin syndrome episodes and compared effects on episode duration with 48 untreated patients with Kleine-Levin syndrome. Mean ages of patients in this study ranged from 16.9–24.6 years and patients were followed for a 3-year period.

The data tables are provided in **Table S72** and **Table S73** in the supplemental material. A summary of findings table is provided in **Table S74** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: disease severity, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Disease severity: The study showed that pre-/post difference in the mean episode duration was 0.1 days (8.2%) lower (95% CI, 5.9 days lower–6.2 days higher) compared to the no-treatment group.[108] This was not a clinically significant reduction. The quality of evidence was rated down to very low due to imprecision (see **Table S72**).

The study also documented a mean pre-/post episode shortening of 19 (46.6%) episodes compared to the no-treatment group. This was a clinically significant reduction. The quality of evidence was rated down to very low due to imprecision (see **Table S73**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and mood. The study identified in our literature review did not report data for fatigue or mood.

Overall quality of evidence

The TF determined that the overall quality of evidence for IV methylprednisolone to treat Kleine-Levin syndrome compared to placebo was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical threshold was met for the critical outcome of disease severity.

Benefits and harms

The TF had insufficient data regarding costs, access, and long-term effects of infusions of IV methylprednisolone.

Nineteen patients (61.3%) in the open-label study of Kleine-Levin syndrome patients on methylprednisolone reported at least 1 adverse effect; the most frequent was an acute, transient insomnia (40%). The other side effects were mild and nondisabling, presenting only during the infusion days. These included insomnia, muscle pain, and nervousness/restlessness, but no mania. None of these symptoms required any specific management.[108]

No other studies included in the systematic review reported on the use of IV methylprednisolone (irrespective of the indication). The balance of risks and harms is likely different for pregnant and breastfeeding women.

Corticosteroids have been shown to be teratogenic in animals. Human data are insufficient to determine risk.

Resource use

Data were unavailable but the TF anticipated that methylprednisolone would have large costs due to the need for IV infusion.

Patient values and preferences

The TF did not believe there was important uncertainty or variability in patient values or preferences for shorter Kleine-Levin syndrome symptomatic bouts or reduced frequency of Kleine-Levin syndrome symptomatic episodes. Overall, the TF felt that

there were moderate desirable anticipated effects and small undesirable effects for use of methylprednisolone therapy in Kleine-Levin syndrome. However, the route of administration may act as a deterrent to preference.

TREATMENT OF HYPERSOMNIA SECONDARY TO MEDICAL DISORDERS, INCLUDING NEUROLOGICAL DISORDERS

The aims of the current literature review and data analyses were focused on addressing the treatment of hypersomnia secondary to medical disorders, including neurological disorders. Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF based on the clinical and pathological subtypes identified in ICSD-3.[2] Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, resource use, and patient values and preferences that contributed to the development of the recommendations provided in the accompanying clinical practice guideline.

The interventions for each clinical and pathological subtype below are listed in alphabetical order.

Hypersomnia secondary to alpha-synucleinopathies

The literature search only identified studies for hypersomnia secondary to Parkinson's disease and dementia with Lewy bodies (DLB) in this subtype. Presented below are summaries of evidence and the statistical analyses for these 2 disorders.

Armodafinil

The TF identified 1 single-arm, open-label pilot study of armodafinil use in patients with hypersomnia secondary to DLB.[109] This 12-week observational study included 17 patients and studied doses ranging from 150–250 mg per day.

The data figures and tables are provided in **Table S75** and **Table S76** in the supplemental material. A summary of findings table is provided in **Table S77** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The 1 single-arm, open-label pilot study of armodafinil use in patients with hypersomnia secondary to DLB showed a clinically significant mean pre-/post reduction of 6.0 points on the ESS (95% CI, 9.0–3.0 points lower).[109] The quality of evidence was very low due to imprecision (see **Table S75**).

The same study demonstrated a clinically significant mean pre- to posttreatment difference on the MWT of 10.4 minutes higher (95% CI, 4.4–16.4 minutes higher). The quality of evidence was very low due to imprecision (see **Table S76**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning or fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for armodafinil for the treatment of hypersomnia secondary to DLB was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.[109]

Benefits and harms

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.

No clinically significant adverse events were observed or reported in the open-label study with patients with DLB.[109]

Across all RCTs included in the systematic review that reported on the use of armodafinil (irrespective of the indication), the risk difference between armodafinil and placebo for headache was 0.13 (95% CI, 0.03–0.20), indicating greater risk of headache for armodafinil[21,23] (see **Figure S66**). Other commonly reported adverse events in the RCTs included nausea (10.7%), upper respiratory tract infection (9%), and dizziness (8.4%). Commonly reported adverse events reported across all observational studies on the use of armodafinil included headache (24.2%), sinusitis (10.2%), somnolence (10.2%), anxiety (8.1%), nausea (8.1%), and nasopharyngitis (8.1%).[22,24] The more serious but rare AEs reported in the product information for armodafinil, such as Stevens-Johnson syndrome, were not detected in the individual studies. The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[110] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of armodafinil in pregnancy. The AASM had reached out to Teva Pharmaceutical Industries Ltd. (makers of modafinil) to gather more information and contacted the FDA requesting that additional guidance be provided for health care professionals in the U.S.

Resource use

Per the NADAC database, the unit cost of 50 and 250 mg doses ranged from $0.26–$1.18.[26] Medication cost to any given

patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF felt that most patients value improvement in excessive daytime sleepiness and there was probably no uncertainty or variability in the outcome measures. In the armodafinil studies, subjective excessive daytime sleepiness did not meet the clinical threshold, but objective measures did. The TF decided that armodafinil provided small benefit and the undesirable effects were also small (mostly headache). Because there was an improvement in the objective measure of excessive daytime sleepiness,[109] the TF felt that patients would most likely favor armodafinil use.

Light therapy

The TF identified 1 RCT of bright-light therapy (vs. dim light) for treatment of subjective excessive daytime sleepiness and fatigue that included 16 participants with Parkinson disease.[111]

The data figures are provided in **Figure S40** and **Figure S41** in the supplemental material. A summary of findings table is provided in **Table S78** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The TF identified 1 RCT for the assessment of excessive daytime sleepiness in patients with hypersomnia secondary to Parkinson's disease using the ESS.[111] The mean difference on the ESS was 1.8 points lower (95% CI, 4.7 points lower–1.1 points higher) with bright light compared to dim light. While results were in favor of bright-light therapy, they did not meet clinical significance. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S40**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning.

Fatigue: The TF identified 1 RCT for the assessment of fatigue in patients with hypersomnia secondary to Parkinson's disease using the Fatigue Severity Scale (FSS).[111] The mean difference on the FSS in the light therapy group was 1.4 points higher (95% CI, 7.5 points lower–10.3 points higher) when compared to the patients receiving dim light. This result did not meet clinical significance. The quality of evidence was downgraded to low for serious imprecision (see **Figure S41**).

Overall quality of evidence

The TF determined that the overall quality of evidence for the use of bright-light therapy to treat hypersomnia secondary to Parkinson's disease compared to dim light was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.[111]

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects was inconclusive in patients with hypersomnia secondary to Parkinson's disease. Two of the 16 patients randomized to bright-light therapy reported 1 adverse effect each: headache and sleepiness; both resolved spontaneously.[111]

Resource use

At the time of this publication, there were no data available on the NADAC website and in the literature review on the cost of light therapy. Cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was possibly important uncertainty regarding whether the majority of patients with hypersomnia due to Parkinson's disease would use light therapy to treat their disease.

Modafinil

The TF identified 4 RCTs that examined the effect of modafinil vs placebo on a total number of 122 adult patients with hypersomnia secondary to Parkinson's disease.[55,56,60,61] The 4 studies had relatively small sample sizes ranging from 12–37 participants and modafinil doses ranging from 50–400 mg/day.

The TF also identified 1 observational study on the effect of modafinil in adult patients with hypersomnia secondary to Parkinson's disease.[64] The sample size in this study was 10. Modafinil doses varied between 100 and 400 mg/day.

The meta-analyses and figures and tables are provided in **Figures S42–S46** and **Table S79** in the supplemental material. A summary of findings table is provided in **Table S80** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. None of the studies identified in our literature review reported data for work/school performance.

Excessive daytime sleepiness: A meta-analysis of 4 RCT studies compared the effect of modafinil to placebo on self-reported excessive daytime sleepiness in patients with Parkinson's disease using the ESS.[55,56,60,61] The meta-analysis showed a clinically significant mean difference of 2.3 points lower (95% CI, 0.7–3.8 points lower) ESS in patients on

modafinil compared to control. The quality of evidence was moderate and downgraded due to imprecision (see **Figure S42**).

A single observational study[64] on the effect of modafinil in patients with Parkinson's disease noted a clinically significant decrease of 8.2 points (95% CI, 4.5–12.0 points lower) on the ESS. The quality of evidence was very low due to imprecision (see **Table S79**).

One RCT compared the effect of modafinil to placebo in patients with Parkinson's disease using the MWT.[56] There was an increase of 1.8 minutes (95% CI, 6.7 minutes lower–10.2 minutes higher) when compared to placebo, which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S43**).

One RCT compared the effect of modafinil to placebo in patients with Parkinson's disease using the MSLT.[60] There was an insignificant clinical change of 0.8 minutes higher (95% CI, 1.5 minutes lower–3.1 minutes higher) when compared to placebo. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S44**).

Quality of life: The TF identified 1 RCT with patients with Parkinson's disease utilizing a total score of the SF-36 to assess quality of life.[60] It demonstrated a reduction of 0.2 points lower (95% CI, 8.3 points lower–7.9 points higher), which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S45**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. None of the studies identified in our literature review reported data for difficulty waking in the morning.

Fatigue: A meta-analysis of 2 RCTs in patients with Parkinson's disease compared the effect of modafinil to placebo on fatigue as measured by the FSS.[55,60] The meta-analyses demonstrated a mean difference of 0.2 points lower (95% CI, 1.3 points lower–0.8 points higher), which was not clinically significant. The quality of evidence was low due to serious imprecision (see **Figure S46**).

Overall quality of evidence

The TF determined that the overall quality of data on modafinil for patients with Parkinson's disease compared to placebo was moderate based on the critical outcomes reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects across all disorders is in favor of modafinil. The use of modafinil demonstrated improvements in quality of life and reductions in daytime sleepiness when compared to placebo.

In patients diagnosed with hypersomnia secondary to Parkinson's disease, the risk difference for the most common adverse events (AEs) reported in the identified RCTs were diarrhea: –0.19 (95% CI, –0.05 to 0.43), cardiac side effects (such as tachycardia/palpations/atrial fibrillation): –0.05 (95% CI, –0.08 to 0.1), and insomnia: –0.04 (95% CI, –0.07 to 0.15). One RCT[61] reported 3 serious AEs of hematuria, 3 AEs of memory loss, and 3 AEs of feeling off balance out of 9 patients with Parkinson's disease. One observational study reported headaches, visual hallucinations, sleep attacks, and generalized tingling (all approximately in 10% of cases).[64] Based on these data, the side effect profile may be higher among patients with Parkinson's than other CNS hypersomnia conditions assessed.

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth: –0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06)[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's efficacy to reduce daytime sleepiness, and its relatively mild side effects. For the most part, the TF determined that patients would likely accept the risk of AEs for this benefit, but this benefit/risk ratio may be lower in the patients with Parkinson's disease given higher rates of more serious AEs reported.

Sodium oxybate

The TF identified 1 randomized, double-blind, placebo-controlled, crossover phase 2a study assessing the effects of sodium oxybate in 12 patients with Parkinson's disease.[87] Doses of sodium oxybate were titrated between 3 g and 9 g per night with a 2- to 4-week washout period. Outcomes assessed in this study included ESS, MSLT, and FSS scores.

The figures and tables are provided in **Figures S47–S49** in the supplemental material. A summary of findings table is provided in **Table S81** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: One RCT[87] reported that patients with Parkinson's disease taking sodium oxybate had a clinically significant mean reduction of 4.2 points lower (95% CI, 2.0–6.4 points lower) on the ESS compared to control. The quality of evidence was moderate due to imprecision (see **Figure S47**).

In the same study, patients also had a clinically significant mean difference on the MSLT of 2.9 minutes higher (95% CI, 1.3–4.5 minutes higher) compared to the placebo group. The quality of evidence was moderate due to imprecision (see **Figure S48**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning.

Fatigue: One RCT[87] reported a mean difference on the FSS of 0.1 points lower (95% CI, 0.7 points lower–0.9 points higher) compared to placebo, which was not clinically significant. The quality of evidence was moderate due to imprecision (see **Figure S49**).

Overall quality of evidence

The TF determined that the overall quality of evidence for treatment of hypersomnia secondary to Parkinson's disease compared to placebo was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF judged that the balance between the desirable and undesirable effects is likely in favor of sodium oxybate for patients with hypersomnia secondary to Parkinson's disease.

All patients with hypersomnia secondary to Parkinson's disease experienced side effects while receiving sodium oxybate.[87] The majority of participants rated these side effects as of mild (not interfering with daily activities; 75% of AEs) or "maximally moderate" (mild to moderate interference; 25% of AEs) intensity and largely resolved after dose adjustment (58% of AEs resolved in 67% of patients). In terms of more serious adverse effects, 17% of patients developed obstructive sleep apnea. Four patients (33%) remained affected by side effects at study termination and none dropped out due to AEs. The risk difference was higher for patients with Parkinson's disease for nausea, diarrhea, chest discomfort, sleep disorders, anxiety/nervousness, and most notably dizziness compared to the overall risk differences across groups. The more serious, but rare, AEs reported in the product information for sodium oxybate, such as respiratory depression, suicidality, and death, were not reported in the individual studies.

Across all RCTs reporting on the use of sodium oxybate, the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances was 0.10 (95% CI, 0.05–0.14), of nausea: 0.10 (95% CI, 0.00–0.21), of dizziness 0.9 (95% CI, 0.04–0.14), of urinary/renal disturbances 0.07 (95% CI, 0.22–0.11), of headache 0.04 (95% CI, –0.17 to 0.08), diarrhea 0.04 (95% CI, –0.01 to 0.10), chest discomfort 0.02 (95% CI, 0.0–0.04), and anxiety or nervousness 0.01 (95% CI, –0.05 to 0.07)[76,78,85,87] (see **Figures S79–S86**). Commonly reported adverse events reported across all observational studies on the use of sodium oxybate included sleep disturbances (22.7%), nausea (20.4%), headache (17.25%), dizziness (17.08%), and confusion (12.8%).[75,79,81,83]

Finally, sodium oxybate 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. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.[88]

Resource use

At the time of this publication, the NADAC did not report on this drug's pricing. Because of the potential risks associated with the drug, it is subject to strict safety controls on prescribing and dispensing under REMS. This drug is only available at certified specialty pharmacies and not in retail pharmacies. Prices are for cash-paying customers only and are not valid with most insurance plans. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was probably no important uncertainty or variability in how patients value the critical outcomes, and the majority of patients with hypersomnia due to medical disorders would likely use sodium oxybate compared to no treatment. Based on available data, sodium oxybate had a large desirable effect on daytime sleepiness and moderate undesirable effects.

Posttraumatic hypersomnia

The literature search only identified studies for hypersomnia associated with traumatic brain injury (TBI) in this subtype. Presented below are summaries of evidence and the statistical analyses for this disorder.

Armodafinil

The TF identified 1 RCT of armodafinil for the treatment of excessive daytime sleepiness as measured by the MSLT and ESS for patients with TBI.[23] This RCT was a 12-week clinical trial with armodafinil doses ranging from 50–250 mg compared to placebo. A total of 104 (n = 27 placebo, n = 77 armodafinil) participants with mostly mild TBI that had occurred 1–10 years prior to study screening completed the study. This study also included an open-label extension with 49 patients to assess the long-term safety and tolerability of armodafinil treatment (results reviewed in the 'Benefits and harms' section below).

The data figures and tables are provided in **Figure S50** and **Figure S51** in the supplemental material. A summary of findings table is provided in **Table S82** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: Based on the RCT,[23] armodafinil use by patients with TBI demonstrated an improvement in mean ESS score in the armodafinil group of 0.7 points greater (95% CI, 3.2 points lower–1.8 points higher improvement) on the ESS compared to placebo. This difference was not clinically significant. The quality of evidence was moderate due to imprecision (see **Figure S50**).

The overall mean sleep latency from baseline to final visit in the above RCT using the MSLT demonstrated a clinically significant improvement in mean MSLT score in the armodafinil group of 2.3 minutes higher (95% CI, 0.4–4.2 minutes higher) compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S51**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning or fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for armodafinil for the treatment of hypersomnia due to TBI compared to placebo was moderate based on the critical outcome reported in the literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.[23]

Benefits and harms

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.

In patients with hypersomnia secondary to traumatic brain injury, the double-blind phase of the RCT reported that 53% of patients receiving armodafinil and 48% of patients receiving placebo experienced at least 1 AE. Headache was the most frequent AE (17%) with a risk difference of 0.15 (95% CI, 0.06–0.24) compared to placebo. This risk difference was comparable to the overall armodafinil meta-analysis of headache side effect across groups of patients with different CNS hypersomnias. Among patients receiving armodafinil, the most frequent reasons for withdrawal due to an AE were headache and anxiety (both 3%) and nausea and dizziness (both 2%). During the open-label phase of armodafinil, 1 patient with TBI developed a moderate psychotic disorder and this resolved after drug discontinuation.[23]

Across all RCTs included in the systematic review that reported on the use of armodafinil (irrespective of the indication), the risk difference between armodafinil and placebo for headache was 0.13 (95% CI, 0.03–0.20), indicating greater risk of headache for armodafinil[21,23] (**Figure S66**). Other commonly reported adverse events in the RCTs included nausea (10.7%), upper respiratory tract infection (9%), and dizziness (8.4%). Commonly reported adverse events reported across all observational studies on the use of armodafinil included headache (24.2%), sinusitis (10.2%), somnolence (10.2%), anxiety (8.1%), nausea (8.1%), and nasopharyngitis (8.1%).[22,24] The more serious but rare AEs reported in the product information for armodafinil, such as Stevens-Johnson syndrome, were not detected in the individual studies.

Finally, 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.110 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of armodafinil in pregnancy.

Resource use

Per the NADAC database, the unit cost of 50 and 250 mg doses ranged from $0.26–$1.18.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF felt that most patients value improvement in excessive daytime sleepiness and there was probably no uncertainty or variability in the outcome measures. In the armodafinil studies, subjective excessive daytime sleepiness did not meet the clinical threshold, but objective measures did. The TF decided that armodafinil provided small benefit and the undesirable effects were also small (mostly headache). Because there was an improvement in objective measures of excessive daytime sleepiness, the TF determined that patients would most likely favor armodafinil use.

Modafinil

The TF identified 1 RCT that examined the effect of modafinil on 20 patients with TBI.[59] Patients received 100 to 200 mg modafinil for a 6-week treatment period.

The meta-analyses and figures and tables are provided in **Figures S52–S54** in the supplemental material. A summary of findings table is provided in **Table S83** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: One RCT compared the effect of modafinil in patients with TBI.[59] The study reported a clinically significant decrease of 3.0 points (95% CI, 1.2–4.8 points lower) on the ESS. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S52**).

One RCT compared the effect of modafinil to placebo in patients with TBI by using the MWT to assess objective sleepiness.[59] There was a clinically significant increase of 8.0 minutes (95% CI, 0.9 to 15.1 minutes higher) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S53**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning.

Fatigue: A single RCT with patients with TBI compared the effect of modafinil to placebo on fatigue as measured by the FSS.[59] The mean change in FSS score in the modafinil group was a clinically significant 0.8 points improvement (95% CI, 0.1–1.5 points improvement) compared to placebo. The quality of evidence was moderate due to imprecision (see **Figure S54**).

Overall quality of evidence

The TF determined that the overall quality of evidence of data on modafinil for patients for the treatment of hypersomnia due to TBI compared to placebo was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects across all disorders is in favor of modafinil. The use of modafinil demonstrated improvements in quality of life and reductions in daytime sleepiness when compared to placebo.

In patients diagnosed with hypersomnia secondary to traumatic brain injury (TBI), the common adverse events reported were nausea (10%) and arthralgia (10%).

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI: –0.02 to 0.04), nausea: –0.05 (95% CI: 0.01 to 0.08), diarrhea: –0.03 (95% CI: 0.00 to 0.06), headache: –0.06 (95% CI: 0.00 to 0.13), dry mouth: –0.02 (95% CI: –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (0.95 CI: 0.01 to 0.08), flu or flu like symptoms: –0.02 (95% CI: –0.03 to 0.07), loss of appetite: −1.03 (95% CI: 0.31 to 5.61) and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI: –0.08 to 0.06).[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's

efficacy to reduce daytime sleepiness, and its relatively mild side effects. For the most part, the TF determined that patients would likely accept the risk of AEs for this benefit.

Genetic disorders associated with primary central nervous system somnolence

The literature search only identified studies for hypersomnia associated with myotonic dystrophy in this subtype. Presented below are summaries of evidence and the statistical analyses for this disorder.

Methylphenidate

The TF identified an RCT assessing the effects of a 20 mg/day dose of methylphenidate on excessive daytime sleepiness in adult participants with myotonic dystrophy compared to placebo.[35] A total of 17 participants completed this randomized, double-blind, placebo-controlled, 3-week crossover trial.

The data figures are provided in **Figure S55** in the supplemental material. A summary of findings table is provided in **Table S84** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The TF identified 1 RCT reporting on excessive daytime sleepiness using the ESS in adult participants with myotonic dystrophy.[35] It demonstrated a mean difference of 1.4 points lower (95% CI, 4.3 points lower–1.6 points higher) in the methylphenidate group when compared to placebo. This was not clinically significant. The quality of evidence was downgraded to moderate for imprecision (see **Figure S55**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning and fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for methylphenidate for the treatment of hypersomnia in adult participants with myotonic dystrophy compared to placebo was moderate based on the critical outcome reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.

Benefits and harms

The TF concluded that the available data was insufficient to provide guidance on the balance of effects of methylphenidate for this patient population.

There was insufficient data to conduct a meta-analysis of methylphenidate side effects in patients with hypersomnia secondary to myotonic dystrophy.[35] Overall, methylphenidate was well tolerated. The aforementioned study reported a total of 9 minor adverse events with methylphenidate, including loss of appetite (11.7%), nausea (5.8%), vomiting (5.8%), and palpitations (5.8%). Three patients discontinued the intervention due to treatment-emergent adverse events (diarrhea, nervousness, and irritability). Overall, the more serious but rare adverse events reported in the product information for methylphenidate such as depression and psychosis were not reported in the included study.[35]

Across the RCTs included in the systematic review that reported on the use of methylphenidate (irrespective of the indication), most adverse events were mild and included loss of appetite (20%) and nausea (10%), vomiting (10%), and palpitations (10%).[35] Commonly reported adverse events reported across all observational studies on the use of methylphenidate included dry mouth (38.6%), sweating (34.9%), headache (24.5%), stomach discomfort (21.6%), and loss of appetite (16.9%).[34] The balance of risks and harms is likely different for pregnant and breastfeeding women.

In addition, this drug 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. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Based on animal data, methylphenidate may cause fetal harm. Human data are insufficient to determine risk. Caution should be exercised if administered to nursing mothers.[36]

Resource use

At the time of this publication, the NADAC reported the drug's pricing ranged from $0.14/mL for solution, $0.12–2.50/tablet (5–20 mg), and $1.95–3.51/capsule (10–60 mg).[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF was uncertain if patients would take the drug over placebo given highly variable results in the RCT and limited data.

Modafinil

The TF identified 2 RCTs that examined the effect of modafinil on patients with myotonic dystrophy. Sample sizes ranged from 19–28 and modafinil doses ranged from 200–300 mg.[112,113]

The meta-analyses and figures and tables are provided in **Figures S56–S62** in the supplemental material. A summary of findings table is provided in **Table S85** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and

work/school performance. None of the studies identified in our literature review reported data for work/school performance.

Excessive daytime sleepiness: A meta-analysis of 2 studies comparing the effect of modafinil in patients with myotonic dystrophy[112,113] demonstrated a clinically significant decrease of 3.6 points (95% CI, 1.5–5.7 points lower) on the ESS. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S56**).

A meta-analysis of 2 studies compared the effect of modafinil to placebo in patients with myotonic dystrophy by using the MWT.[112,113] There was a clinically significant increase of 5.8 minutes (95% CI, 4.6 minutes lower–16.2 minutes higher) when compared to placebo. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S57**).

One RCT compared the effect of modafinil to placebo in patients with myotonic dystrophy using the MSLT,[112] reporting a change of 0.3 minutes lower (95% CI, 3.8 minutes higher–4.3 minutes lower) when compared to placebo, which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S58**).

Quality of life: One RCT with patients with myotonic dystrophy[112] utilizing a total score of the SF-36 reported a reduction of 1.2 points (95% CI, 6.1 points lower–3.8 points higher), which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S59**).

Another RCT with patients with myotonic dystrophy[113] demonstrated a reduction in the mean difference for the mental component of the SF-36 of 0.3 points (95% CI, 8.5 points lower–7.8 points higher) and a mean difference for the SF-36 physical component of 2.4 points higher (95% CI, 8.0 points lower–12.9 points higher). Neither the mental nor physical component scores met clinical significance. The quality of evidence was downgraded to low due to serious imprecision (see **Figure S60** and **Figure S61**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. None of the studies identified in our literature review reported data for difficulty waking in the morning.

Fatigue: One RCT in patients with myotonic dystrophy reported the SF-36 energy and vitality component score.[113] The study reported a clinically significant mean increase of 10.7 points (95% CI, 1.1 points lower–22.5 points higher). The quality of evidence was moderate due to imprecision (see **Figure S62**).

Overall quality of evidence

The TF determined that the overall quality of evidence of data on modafinil for patients with hypersomnia secondary to myotonic dystrophy compared to placebo was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for the critical outcomes: excessive daytime sleepiness and disease severity.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects is in favor of modafinil. The use of modafinil demonstrated improvements in quality of life and reductions in daytime sleepiness when compared to placebo.

In patients diagnosed with hypersomnia secondary to myotonic dystrophy, 1 RCT[112] reported the following adverse events: diarrhea, insomnia, spatial disorientation, acne, and weight loss (in about 8% of the patients). The drug was well tolerated with no adverse effects in patients within the study. In addition, no patient stopped either the active drug or placebo because of unwanted effects.[113]

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth: –0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06)[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's efficacy to reduce daytime sleepiness and its relatively mild side

effects. For the most part, the TF determined that patients would likely accept the risk of AEs for this benefit.

Selegiline

The TF identified 1 RCT with a total of 20 adult participants with myotonic dystrophy.[114] The dose of selegiline was 20 mg.

The figure is provided in **Figure S63** in the supplemental material. A summary of findings table is provided in **Table S86** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: One study reported on this outcome using the MSLT.[114] The study did not demonstrate a clinically significant improvement in favor of selegiline. The mean difference between selegiline and placebo was 3.7 minutes lower on the MSLT (95% CI, 8.8 minutes lower–1.4 minutes higher), indicating that selegiline made patients sleepier than control patients. The quality of evidence was rated moderate due to imprecision (see **Figure S63**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning or fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for selegiline treatment of hypersomnia due to myotonic dystrophy compared to placebo was low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome of excessive daytime sleepiness.

Benefits and harms

The TF determined that the balance between desirable and undesirable effects was inconclusive. The single RCT reported no serious adverse effects or adverse effects that resulted in discontinuation of the study drug.

In patients with hypersomnia secondary to myotonic dystrophy, 20% of patients reported irritability and 10% of male patients had difficulty with micturition.[114] The more serious but rare AEs reported in the product information for selegiline, such as hypertensive crisis, arrhythmias, and mental status alterations, were not reported in the individual study.

Across all RCTs included in the systematic review that reported on the use of selegiline (irrespective of the indication), side effects included irritability (20%), slight difficulty in micturition (10%), and headache (10%).[72,114] The adverse events required neither treatments nor the interruption of the study drug. Commonly reported adverse events reported in the observational study identified on the use of selegiline included headache (13%) and irritability (5%).[32] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, selegiline is a monoamine oxidase-B inhibitor and should not be taken with medications that could result in serotonin syndrome (eg, SSRIs). Based on animal data, selegiline may cause fetal harm. Human data are insufficient to determine risk.

Resource use

At the time of this publication, there were no data available on the NADAC website on this drug's price. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF felt that there was probably important uncertainty or variability in patient values and preferences for this particular treatment. Undesirable effects were moderate with the potential to change to severe effects.

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

The literature search only identified studies for hypersomnia associated with multiple sclerosis in this subtype. Presented below are summaries of evidence obtained and the statistical analyses for this disorder.

Modafinil

The TF identified 1 prospective 3-month, open-label study on the effect of modafinil in 47 adult patients with hypersomnia secondary to multiple sclerosis.[115] Modafinil doses varied between 100 and 400 mg/day.

The data tables are provided in **Table S87** and **Table S88** in the supplemental material. A summary of findings table is provided in **Table S89** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: A single observational study on the effect of modafinil in adult patients with hypersomnia secondary to multiple sclerosis noted a clinically significant decrease of 4.8 points (95% CI, 3.4–6.2 points lower) on the ESS.[115] The quality of evidence was very low due to imprecision. (see **Table S87**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when

recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning.

Fatigue: A single observational study of patients with multiple sclerosis showed a clinically significant reduction of 4.9 points (95% CI, 2.3–7.6 points lower) on the FSS.[115] The quality of evidence was very low due to imprecision (see **Table S88**).

Overall quality of evidence

The TF determined that the overall quality of evidence of data on modafinil for patients with hypersomnia secondary to multiple sclerosis was very low based on the critical outcome reported in the literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome: excessive daytime sleepiness.

Benefits and harms

Patients with multiple sclerosis appeared to tolerate modafinil at relatively low doses, according to an open-label study.[115] Around 6% of patients stopped the treatment due to restlessness, nervousness, and aggravation of pre-existent vertigo.

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth: –0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06)[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Finally, 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.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was probably no important uncertainty or variability in how patients value the critical outcomes and concluded that the majority of patients would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's efficacy to reduce daytime sleepiness and its relatively mild side effects.

Hypersomnia secondary to endocrine disorder

The literature search only identified studies for hypersomnia secondary to type 2 diabetes mellitus (type 2 DM) in this subtype. Presented below are summaries of evidence and the statistical analyses for hypersomnia secondary to this disorder.

Liraglutide

The TF identified 1 open-label retrospective study of injectable liraglutide for the treatment of excessive daytime sleepiness in 158 adult patients with type 2 DM.[116] This study reported the pre- and posttreatment effect of liraglutide in 158 patients over a 3-month period.

The data tables are provided in **Table S90** in the supplemental material. A summary of findings table is provided in **Table S91** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The TF identified 1 observational study for the assessment of excessive daytime sleepiness using the ESS.[116] After 3 months of treatment, patients with type 2 DM had a mean ESS reduction of 1.5 points (95% CI, 0.6–2.4 points lower) with use of liraglutide compared to pretreatment. This difference did not meet the clinical significance threshold. The quality of evidence was very low due to imprecision (see **Table S90**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning or fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for liraglutide for the treatment of hypersomnia in patients with type 2 DM was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.[116]

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects is inconclusive. The use of liraglutide in adult patients with type 2 DM did not demonstrate an

improvement in any of the critical outcomes. Side effects were not mentioned in the manuscript. The balance of risks and harms is likely different for pregnant and breastfeeding women.

No other studies included in the systematic review reported on the use of liraglutide (irrespective of the indication). Based on animal data, liraglutide may cause fetal harm.

Resource use

At the time of this publication, the NADAC reported on this drug's price for brand names of liraglutide: Saxenda as $76.93/mL and Victoza as $92.83/mL.[26] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was possibly important uncertainty regarding whether or not the majority of patients would use liraglutide to treat their hypersomnia secondary to type 2 DM.

TREATMENT OF HYPERSOMNIA ASSOCIATED WITH A PSYCHIATRIC DISORDER

The aims of the current literature review and data analyses were focused on addressing the treatment of hypersomnia associated with a psychiatric disorder. Only studies for either seasonal affective disorder (SAD) or major depressive disorder (MDD) were found and reviewed.

Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, resource use, and patient values and preferences that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. The interventions below are listed in alphabetical order.

Light therapy

The TF identified 1 RCT that examined the effect of light therapy on a total number of 16 female adult patients with winter seasonal affective disorder (SAD) in comparison to adult female healthy control patients (n = 13).[117] All subjects were free of "any regular psychotropic medication" for ≥ 1 year prior to study entry.

Seven patients with SAD received light therapy for 60 minutes daily, and 9 patients with SAD and 8 control patients received light therapy for 15 minutes daily, for a period of 14 days. Measured illumination was approximately 3300 lux at eye level. Patients received standardized instructions for behaviors during the treatment protocol.

The table is provided in **Table S92** in the supplemental material. A summary of findings table is provided in **Table S93** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. The study identified in our literature review did not report data for quality of life or work/school performance.

Excessive daytime sleepiness: The above study reported on this outcome. Subjective sleepiness was measured with the Stanford Sleepiness Scale (SSS) on an hourly basis posttreatment. The TF compared the pooled baseline data with the pooled postintervention data. The pre-/post difference was 0.9 points lower (95% CI, 0.3–1.5 points lower). This was not clinically significant. The evidence was downgraded to moderate due to imprecision (see **Table S92**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. The study identified in our literature review did not report data for difficulty waking in the morning or fatigue.

Overall quality of evidence

The TF determined that the overall quality of evidence for the use of light therapy for those with hypersomnia in association with psychiatric disorders (specifically SAD) was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was not met for the critical outcome. Gleaned data may not be generalizable to male populations, as only females were included in the sole identified study.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects in these patients was inconclusive. There was no reporting of adverse effects in this study. Overall, the TF felt that light therapy had trivial undesirable anticipated effects.

Resource use

At the time of this publication, there were no data available on the NADAC website and in the literature review on the cost of light therapy. Cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined that there was possibly important uncertainty regarding whether or not the majority of patients with hypersomnia associated with a psychiatric disorder would use light therapy to treat their disease.

Modafinil

The TF identified 2 RCTs that examined the effect of modafinil vs placebo on a total number of 208 adult patients with hypersomnia (and/or fatigue) in association with major depressive disorder (MDD).[57,58] In the double-blind, placebo-controlled parallel-group investigation[57] (n = 72), modafinil was used adjunctively with a selective serotonin reuptake inhibitor (SSRI) among patients with coexisting sleepiness *and* fatigue. In the

other double-blind, placebo-controlled study (n = 136),[58] the authors utilized the same parameters as primary outcomes (ESS and FSS). These 2 RCTs had modest sample sizes ranging from 72–136 and used modafinil doses ranging from 100–400 mg.

The TF also identified 2 open-label studies of adult patients (n = 60) with hypersomnia (and/or fatigue) in association with MDD.[65,118] The first study[118] (n = 31) comprised of patients with partially remitted MDD. The primary outcome measures were solely designed to address fatigue. Patients continued to receive their standard antidepressant therapy and used modafinil at doses ranging from 100–400 mg.

The second study[65] (n = 29) comprised of patients with active depression. These 2 studies had relatively small sample sizes ranging from 29–31 and used modafinil doses that ranged from 100–400 mg.

The figures and tables are provided in **Figure S64** and **Tables S94–S97** in the supplemental material. A summary of findings table is provided in **Table S98** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, quality of life, and work/school performance. None of the studies identified in our literature review reported data for work/school performance.

Excessive daytime sleepiness: One RCT compared the effect of modafinil to placebo in 72 patients with excessive daytime sleepiness and MDD.[57] The data demonstrated a clinically insignificant mean ESS difference of 0.8 points lower (95% CI, 2.7 points lower–1.1 points higher) in the modafinil group when compared to placebo over a treatment period of 6 weeks (see **Figure S64**).

In the other RCT,[58] 136 patients with partially treated MDD received 100 mg modafinil on days 1–3 and 200 mg on days 4–7, with flexible dosing thereafter (maximum daily dosage of 400 mg) during a 6-week treatment period. The study solely provided baseline ESS data, but postintervention data were displayed in a figure. The estimated calculations demonstrated a clinically insignificant mean ESS difference of 1.7 points lower (95% CI, 0.6–2.8 points lower) at week 6. The quality of evidence based on these 2 studies was considered moderate due to imprecision (see **Table S94**).

One open-label study conducted weekly ESS evaluations for a period of 6 weeks among 29 patients with MDD.[65] Modafinil was initiated at a dose of 100 mg/day for days 1–3 and titrated from day 4 to a maximum dose of 200 mg/day. If "clinically indicated," the modafinil dosage was reduced to 100 mg/day or changed to 100 mg twice daily. Only baseline raw data were provided. The post 6-week treatment data were displayed in a figure. Estimated calculations demonstrated a clinically significant mean pre-/post difference of 5.5 points lower (95% CI, 2.6–8.4 points lower) in the ESS at the study endpoint. The quality of evidence was considered very low due to imprecision (see **Table S95**).

Quality of life: An open-label study of patients with MDD and fatigue ± sleepiness conducted weekly evaluations for a period of 6 weeks.[65] Only posttreatment data were provided for the SF-36 physical and mental component summaries. Data reported were not suitable for analysis.

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: difficulty waking in the morning and fatigue. None of the studies identified in our literature review reported data for difficulty waking in the morning.

Fatigue: One RCT[57] measured the effects of modafinil on fatigue in patients with MDD with the FSS. There was a clinically insignificant improvement of a 0.1 point reduction (95% CI, 0.9 points lower–0.7 points higher) with modafinil group than with the placebo group. The quality of evidence was deemed low and was downgraded due to serious imprecision (see **Figure S65**).

The other RCT[58] comprised of patients with partially treated MDD, the majority of whom (82%) were fatigued. The publication provided baseline FSS data and the post-6-week treatment data were displayed in a figure. The estimated change score was a 0.30 decrease. This was not clinically significant. The quality of evidence was downgraded to moderate due to imprecision (see **Table S96**).

Fatigue was also evaluated using the FSS in an open-label study of patients with MDD.[65] Estimated calculations demonstrated a clinically significant mean FSS difference of 2.2 points lower (95% CI, 1.2–3.2 points lower) at the study endpoint. The quality of evidence was very low due to imprecision (see **Table S97**).

Overall quality of evidence

The TF determined that the overall quality of evidence for the use of modafinil for those with hypersomnia associated with MDD compared to placebo was moderate based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was not met for the critical outcome.

Benefits and harms

The TF determined that the balance between the desirable and undesirable effects was inconclusive. In patients with hypersomnia associated with MDD, the use of modafinil demonstrated reductions in daytime sleepiness and fatigue when compared to placebo.

Most adverse events in patients with hypersomnia associated with MDD were mild, including insomnia, nausea, abdominal pain, constipation, and diarrhea. Compilation of data from the 2 RCTs[57,58] suggested a higher incidence of headache (11%) and anxiety/nervousness (12%) associated with modafinil among those with MDD in association with sleepiness and/or fatigue. Two patients with suicidal ideation were reported in Dunlop et al[57] (1 reported a serious adverse event because hospitalization was required).

Across all RCTs that reported on the use of modafinil (irrespective of the indication), the risk difference of the commonly reported adverse effects between modafinil and placebo were as follows: insomnia: –0.01 (95% CI, –0.02 to 0.04), nausea: –0.05 (95% CI, 0.01–0.08), diarrhea: –0.03 (95% CI, 0.00–0.06), headache: –0.06 (95% CI, 0.00–0.13), dry mouth:

–0.02 (95% CI, –0.02 to 0.07), anxiety or nervousness or panic attacks: –0.04 (95% CI, 0.01–0.08), flu or flu-like symptoms: –0.02 (95% CI, –0.03 to 0.07), loss of appetite: –1.03 (95% CI, 0.31–5.61), and tachycardia/palpitations/atrial fibrillation: –0.01 (95% CI, –0.08 to 0.06)[44,46,51,54–62] (see **Figures S67–S75**). Across all observational studies reporting on the use of modafinil, the commonly reported adverse events included headache (26%), insomnia (8.4%), nausea (8.1%), dry mouth (5.6%), and diarrhea (2.6%).[39,47,63–65] The balance of risks and harms is likely different for pregnant and breastfeeding women.

Based on animal data, modafinil may cause fetal harm. Human data are insufficient to determine risk.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

In general, cost-effectiveness analyses have demonstrated that modafinil is a cost-effective therapy compared to no therapy. At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.26 Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

No specific data exist related to patient values and preferences with respect to the use of modafinil among those with sleepiness associated with a psychiatric disorder and there is heterogeneity among the patient populations identified. There were insufficient data to determine patient values for or against treatment.

THE TREATMENT OF NARCOLEPSY IN PEDIATRIC POPULATIONS

The aims of the current literature review and data analyses were focused on addressing the treatment of narcolepsy in pediatric populations. Review of the literature did not produce relevant data meeting inclusion criteria regarding treatments commonly used in pediatric narcolepsy such as methylphenidate, amphetamines, scheduled naps, and SSRI/SNRI medications (for cataplexy). Below are detailed summaries of the evidence identified in the literature searches and the statistical analyses performed by the TF. Each evidence summary is accompanied by a discussion of the quality of evidence, balance of benefits and harms, patient values and preferences, and resource use considerations that contributed to the development of the recommendations provided in the accompanying clinical practice guideline. The interventions below are listed in alphabetical order.

Modafinil

The TF identified 1 observational study that examined the effect of modafinil in pediatric patients with narcolepsy type 1. The average age at diagnosis was 11.8 ± 3.3 years.[119]

The tables are provided in **Table S99** and **Table S100** in the supplemental material. A summary of findings table is provided in **Table S101** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for cataplexy, quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: One observational study reported on changes in daytime sleepiness using the ESS in pediatric patients with NT1.[119] The mean pre-/post ESS score in patients with NT1 on modafinil demonstrated a clinically significant improvement of 6.2 points lower (95% CI, 3.9–8.5 points lower). The quality of evidence was very low due to imprecision (see **Table S99**).

The aforementioned observational study also assessed sleepiness using the MSLT. The mean MSLT score in the pediatric patients was 0.4 minutes higher (95% CI, 0.3 minutes lower–1.2 minutes higher).[119] This was not clinically significant. The quality of evidence was very low due to imprecision (see **Table S100**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for modafinil for the treatment of narcolepsy in pediatric patients was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. The clinical threshold was met for the critical outcome: excessive daytime sleepiness.

Benefits and harms

The TF concluded that the balance between the desirable and undesirable effects is likely in favor of modafinil in pediatric populations. The use of modafinil demonstrated reductions in daytime sleepiness and improvements in disease severity when compared to placebo and in observational studies.

In patients with narcolepsy, irritability was the most common side effect. Other side effects included dry mouth, nausea, and headaches. Loss of appetite was noted to be from 0%–10%. No severe reactions were reported. Reported cases of psychosis and Stevens-Johnson syndrome (severe) have limited FDA approval of modafinil for patients over 17 years of age. The balance of risks and harms is likely different for pregnant and breastfeeding patients.

Finally, 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.[105] 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.[25] Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

Resource use

In general, cost-effectiveness analyses have demonstrated that modafinil is a cost-effective therapy compared to no therapy. At the time of this publication, per the NADAC database, the unit cost of 100–200 mg doses ranged from $0.92–$1.02 for each tablet.[105] Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF determined there was no important uncertainty or variability in how patients or their caregivers value the critical outcomes and concluded that the majority of parents of pediatric patients would likely use modafinil when compared to no treatment. This assessment reflects the TF's clinical judgment, based on modafinil's efficacy to reduce daytime sleepiness, and its relatively mild side effects.

Sodium oxybate

The TF identified 1 prospective double-blind, placebo-controlled, randomized-withdrawal, multisite study and subsequent open-label follow-up study (age range, 7–17 years) that examined changes in daytime sleepiness, disease severity, and weekly cataplexy episodes in pediatric patients with NT1.[121]

The literature search also identified 3 observational studies examining the effect of sodium oxybate in pediatric patients with NT1.[122–124]Sample sizes varied between 10 and 31 and sodium oxybate doses were in the 5 ± 2 g range.

The meta-analyses and figures and tables are provided in **Figure S91** and **Figure S92** and **Tables S102–S106** in the supplemental material. A summary of findings table is provided in **Table S107** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. None of the studies identified in our literature review reported data for quality of life, accident risk, or work/school performance.

Excessive daytime sleepiness: The single RCT-withdrawal study examined the effect of sodium oxybate to placebo to compare changes in daytime sleepiness in a pediatric population with NT1 using the ESS for Children and Adolescents (ESS-CHAD) in 63 of the 104 participants.[121] The mean ESS-CHAD score in pediatric patients with NT1 on sodium oxybate was clinically significant at 2.7 points lower (95% CI, 1.3–4.0 points lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S90**).

Two observational studies[122,124] also showed a clinically significant pre-/post difference of 5.4 points to 6.9 points lower in the mean ESS-CHAD. The quality of evidence was very low due to imprecision (see **Table S102**).

One observational study conducted the assessment of sleepiness by using the MSLT.[123] The mean MSLT score in the pediatric patients on sodium oxybate (n = 13) was a clinically significant difference at 1.8 minutes higher (95% CI, 0.8 minutes lower–4.4 minutes higher). The quality of evidence was very low due to imprecision (see **Table S103**).

Cataplexy: One RCT evaluated the change in weekly cataplexy episodes after the withdrawal of sodium oxybate in pediatric patients with NT1 using sleep diaries.[121] The study demonstrated a clinically significant 327.3% increase in the weekly cataplexy rate following the abrupt cessation of sodium oxybate therapy in these patients when compared with those who continued the drug. This increase was clinically significant. The quality of evidence was moderate due to imprecision (see **Table S104**).

One observational study reported on the change in weekly cataplexy episodes in response to sodium oxybate for a period of 3–90 months in 14 pediatric patients using sleep diaries.[124] The percentage difference in mean cataplexy reduction was noted to be 93.9% when compared with placebo. The quality of evidence was very low due to imprecision (see **Table S105**).

Another observational study reported on the change in daily cataplexy episodes in response to sodium oxybate for a period of 3 months in 13 pediatric patients using sleep diaries.[123] The percentage difference in mean cataplexy reduction was noted to be 94.8% when compared with placebo. The quality of evidence was very low due to imprecision (see **Table S106**).

Disease severity: One RCT reported on disease severity based on the CGI-C (cataplexy severity) score. The mean score in pediatric patients with narcolepsy in the withdrawal group was 1.1 points worse (95% CI: 0.5 points–1.7 points higher) compared to those who remained on the sodium oxybate. The quality of evidence was downgraded to moderate due to imprecision (see **Figure S91**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. None of the studies identified in our literature review reported data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the overall quality of evidence for sodium oxybate for the treatment of narcolepsy in pediatric populations was moderate based on the critical outcomes reported in the literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were met for

the critical outcomes: excessive daytime sleepiness, cataplexy, and disease severity. All studies were of brief duration (weeks to months); hence it is not possible to gauge the effect of long-term benefits and side effects of sodium oxybate.

Benefits and harms

The TF concluded that the balance was probably in favor of sodium oxybate as it demonstrated moderate desirable outcomes and moderate undesirable outcomes.

In publications that reported on adverse events of sodium oxybate in pediatric patients, 1 study observed weight loss in about 10% of the patients. This is of moderate concern as the TF noted that obesity is a common comorbidity of narcolepsy and some weight loss may be a desirable effect.[121] Central sleep apnea with AHI > 10 events/h was seen in 6% of the patients. Other commonly reported adverse events were enuresis (21% of sodium oxybate–naïve participants vs 13% of participants taking sodium oxybate at study entry), nausea (22% vs 6%), vomiting (21% vs 6%), headache (18% vs 13%), decreased weight (15% vs 3%), decreased appetite (11% vs none), nasopharyngitis (10% vs none), and dizziness (7% vs 3%). There were 2 serious AEs, one with psychosis and another with suicidal tendencies. In another study, side effects were seen in 40% of the patients and included tremor, blurred vision, increased night awakenings, and nightmares. Thirteen percent discontinued sodium oxybate therapy due to nausea, constipation, and dissociative feelings.[124] The balance of risks and harms is likely different for pregnant and breastfeeding patients.

The U.S. label for sodium oxybate 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. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.[88]

Resource use

At the time of this publication, the NADAC did not report on this drug's pricing. This drug is only available at certified specialty pharmacies and not in retail pharmacies. According to the price guide on https://www.drugs.com, the cost for cash-paying patients of sodium oxybate oral liquid (500 mg/mL) is around $4,829 for a supply of 180 mL, depending on the pharmacy patients visit. Prices are for cash paying customers only and are not valid with most insurance plans. Medication cost to any given patient is uncertain and determined by insurance coverage, copays, and deductibles.

Patient values and preferences

The TF concluded that there was probably no uncertainty or variability in the outcome measures and that the majority of parents of pediatric patients with narcolepsy would likely use sodium oxybate compared to no treatment. Based on available data, sodium oxybate had a desirable effect on daily and weekly cataplexy rates and daytime sleepiness.

Intravenous immune globulin (IVIG)

The TF's review of the literature identified 1 nonrandomized, open-label, controlled, longitudinal observational study of IVIG use in pediatric narcolepsy patients with (n = 22) compared to controls (n = 30).[125]

The table is provided in **Table S108** in the supplemental material. A summary of findings table is provided in **Table S109** in the supplemental material. A summary of the evidence for each outcome is provided below.

Critical outcomes

The following outcomes were determined by the TF to be critical for decision-making when recommending the use of this intervention: excessive daytime sleepiness, cataplexy, disease severity, quality of life, accident risk, and work/school performance. The study identified in our literature review did not report data for excessive daytime sleepiness, quality of life, accident risk, or work/school performance.

Cataplexy: IVIG was not associated with a change on the Clinical Global Impression scale for cataplexy (CGI-C) measured at multiple time points up to 2 years following IVIG treatment.[125]

Disease severity: The Clinical Global Impression scale for sleepiness (CGI-S) was rated by clinicians to capture the severity of daytime sleepiness in this study. The mean CGI-S score pre-/post difference in the IVIG group was an estimated 0.7 points higher (95% CI, 0.3–1.0 points higher). This was not clinically significant. The quality of evidence was downgraded to very low due to imprecision (see **Table S108**).

Important outcomes

The following outcomes were determined by the TF to be important outcomes but not critical for decision-making when recommending the use of this intervention: fatigue and sleep quality. The study identified in our literature review did not report data for fatigue or sleep quality.

Overall quality of evidence

The TF determined that the quality of evidence for IVIG for the treatment of narcolepsy in pediatric patients was very low based on the critical outcome reported in literature and downgrading the quality of evidence because of imprecision. Clinical thresholds were not met for the critical outcomes.

Benefits and harms

The use of IVIG demonstrated minimal improvements in disease severity on the CGI-S scale but was not clinically significant. It demonstrated no other beneficial effects on narcolepsy symptoms. There was no mention of medication side effects.

The balance of risks and harms is likely different for pregnant and breastfeeding patients. Insufficient animal and human data exist to determine risk.

Resource use

Although detailed cost information is not available, direct costs of IVIG therapy will potentially be high due to medication and nurse labor costs and indirect costs such as the necessity of an infusion center or hospitalization to receive this treatment option.

Patient values and preferences

The TF felt that there was probably no important uncertainty or variability in how people value the main outcomes. But there were insufficient data to determine patient values for or against treatment. IVIG treatment requires visits to an infusion center or hospitalization and placement of an IV. The time, effort, discomfort, and lack of benefit associated with this therapy are likely to reduce enthusiasm for this treatment.

DISCUSSION AND FUTURE DIRECTIONS

This systematic review provides a current assessment of the evidence of treatment efficacy for disorders of hypersomnolence, to assist in clinical decision-making and to highlight remaining knowledge gaps for some medications and conditions. The TF assessed the evidence using GRADE for the purposes of making clinical practice recommendations. This approach offers a rigorous, patient-centered, transparent system of evaluation. While the TF intends this analysis to be a useful guide for health care providers in discussing and recommending evidence-based treatments for patients with CNS disorders of hypersomnolence, it is not intended to prohibit or advise against use of medications for which there are currently insufficient data for a GRADE recommendation. The absence of a recommendation, as listed in the accompanying clinical practice guideline, only implies an absence of data; it does not necessarily imply the absence of a clinical benefit. Rather, this evidence-based guide should serve to highlight the areas in which data are still insufficient for evidence-based decision-making.

Because most CNS disorders of hypersomnolence conditions are rare or infrequently studied, the TF anticipated finding only small, methodologically limited studies for some treatments. Thus, the TF chose to include studies with $n \geq 10$ participants. The TF prioritized evidence from large randomized controlled studies when available but also included clinical research studies with less-robust study designs. The TF downgraded evidence quality for imprecision or small sample size ($n < 100$) once (eg, downgrading high to moderate) but did not downgrade twice (eg, downgrading high to low) unless imprecision was very serious. The TF did not downgrade evidence solely because of pharmaceutical funding, as long as there was no evidence of biased design or reporting. Last, due to a lack of comparative effectiveness studies assessing efficacy and safety between different treatments, the TF cannot comment on which medications should be used "first" or "second" line.

CHALLENGES OF ASSESSING TREATMENT EFFICACY

Assessment of CNS disorders of hypersomnolence treatment efficacy is a complex task requiring clinical expertise and patient input. These challenges are listed below. There were many treatments (for example SSRI/SNRI medications for cataplexy) for which guidelines could not be developed due to limited/insufficient data or because supporting studies did not meet inclusion criteria. The TF's inability to issue guidelines in these cases should not be construed as a recommendation against their use.

- Limited data exist addressing patient values and the outcome measures that patients and caregivers prioritize most highly. The TF prespecified outcome measures for critical and important outcomes based on stakeholder input, clinical experience of TF members, and availability of outcomes in the literature.
- Many identified studies (particularly older studies) did not use validated outcome measures limiting interpretation and meta-analysis and thus were excluded from review. As a result, some interventions recommended in a prior practice parameter[10] or widely used in clinical practice could not be addressed in this review, such as SSRIs/SNRIs for cataplexy associated with NT1 or traditional stimulants for idiopathic hypersomnia.
- Sleep inertia is a significantly disabling symptom of idiopathic hypersomnia that impacts quality of life and has not been systematically evaluated.
- The TF could not analyze cost-effectiveness and efficacy from the standpoint of patient preference because this information is simply unavailable for most drugs.
- Lifestyle issues such as diet and exercise, which also impact sleepiness and the quality of life, have not been systematically studied.
- For some agents, eg solriamfetol, the maximum FDA approved dose (150 mg daily) may differ from the maximally studied dose (300 mg daily) in the clinical trial.
- Measures of specified outcomes such as excessive daytime sleepiness varied substantially from study to study and consisted of both subjective assessments like the ESS and CGIs and objective measures such as the MSLT and MWT. When both subjective and objective measures were included, uncertainty existed about whether to place greater weight on subjective or objective assessments, because they do not correlate consistently[49,50] and in some cases were disproportionately affected by a particular treatment. Multiple studies included the MSLT as a primary objective outcome measure. The MSLT, while important for diagnosis, is less relevant as an outcome measure because increases in sleep latency when attempting to nap are not as important as the ability to remain awake, as measured by the MWT.
- Studies on children may involve parental bias in documenting sleepiness and cataplexy. Further, the

MWT has not been validated in children and adolescents.
- The assessment of cataplexy relied on nonstandard and subjective measures like sleep diaries.
- Two of the 4 components of GRADE, ie, patient values and preferences and resource use, have been addressed on a limited scale in literature, which has posed a challenge in formulating treatment recommendations.
- Other critical outcomes, including absenteeism and presenteeism at school and work, were not assessed by any studies. Some of these same outcomes currently lack validated measures assessing treatment response (ie, clomipramine for cataplexy), hampering their inclusion in future treatment trials. There is a clear need for better outcome measures that include work, school, and social function as well as safety domains.
- When available, the TF based the clinical significance thresholds (CSTs) on published literature. When such data were lacking, the TF created CSTs based on their collective clinical experience. Such thresholds were typically conservative because the TF desired to identify even modest treatment effects.
- With regard to the sodium oxybate double-blind, placebo-controlled, randomized-withdrawal clinical trial for the treatment of pediatric narcolepsy, the TF found it difficult to evaluate the clinical effect when the study drug was abruptly withdrawn compared to a standard RCT presenting comparison data of the study drug compared to placebo.
- There were no clinical trials for commonly used treatments in pediatric narcolepsy (methylphenidate/amphetamines/scheduled naps).
- Outcome measures such as fatigue scales are not yet validated among patients with CNS hypersomnia conditions, making it possible that smaller benefits are clinically meaningful in these groups. GRADE focuses heavily on patient values, highlighting the need for validated adult and pediatric patient reported outcomes (PROs) for CNS hypersomnia conditions. Such PROs would anchor CSTs on current outcome measures ensuring that guideline documents focus on aspects of disease mattering most to patients.
- Challenges arose when assessing treatment efficacy by hypersomnia diagnosis. The TF recognizes that NT1 and NT2 are 2 distinct conditions with different pathophysiology[126] and significant variability in symptomology.[6,127] However, most narcolepsy studies included patients with both disorders, and many failed to provide separate data for the 2 diseases. The TF therefore decided to assess quality of evidence based on combined data for both types of narcolepsy, reporting disease-specific data when available. It should not be concluded that people with either type of narcolepsy will necessarily respond similarly to a given medication. Going forward, the TF hopes that the diagnostic certainty of these disorders can improve so future trials can be done with more homogeneous study groups.
- For studies lumping CNS disorders of hypersomnolence participants together and for which data were reported in aggregate (eg, clarithromycin for NT2 or idiopathic hypersomnia), only disease-specific data were used for this review. If disease-specific data could not be obtained (eg, modafinil for NT1, NT2, or idiopathic hypersomnia), the study was excluded.
- 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.

LIMITATIONS OF RECOMMENDATIONS

This review had several limitations. Data reporting in individual studies was often insufficient for inclusion in meta-analysis of treatment effects. In all cases of incomplete reported data, the study authors were contacted, but fewer than 5% responded with requested data. Meta-analyses were at times biased toward the null because they included nontherapeutic medication doses (eg, sodium oxybate for narcolepsy). There were also insufficient data in most studies to perform meta-analysis of adverse effects. Many included studies were small, which limits the ability to detect rare but serious adverse events. A more recent study of over 337,000 adolescents and young adults treated for attention-deficit hyperactivity disorder (ADHD) demonstrated a significantly higher risk of new-onset psychosis with amphetamines than with methylphenidate (although the overall magnitude of risk was low enough at 2.4 patients per 1,000 person-years).[128] Thus, practitioners are advised to carefully evaluate current general adverse effects of treatments in the context of individual patient needs. Information on postmarketing adverse effects are not available for newer treatments such as pitolisant and solriamfetol, further limiting risk/benefit assessments. Last, the TF did not assess clinical trials combining treatments and recognizes that additive benefits and risks may be present with such management.

When available, drug pricing from NADAC was reported. Unfortunately, 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 could not identify studies assessing the cost:benefit ratio for most medications. Thus, the cost of medications was de-emphasized in TF treatment assessments.

For several conditions and for pediatric patients, very few studies were identified, highlighting a clear need for further research.

FUTURE RESEARCH DIRECTIONS

In the course of the systematic review of the literature, the TF found a paucity of comparative effectiveness studies. As new

medications enter the market, researchers are encouraged to compare medications against standard treatments so that physicians and patients can factor this information into treatment decisions. Similarly, the field must fund and perform well-designed studies evaluating commonly used traditional stimulants for central disorders of hypersomnolence and SSRI/SNRI cataplexy treatments for patients with NT1. For instance, a prospective clinical trial is needed for venlafaxine, a drug widely used for treating cataplexy. The low cost of these therapies is attractive, and these treatments are already commonly used across the world. As promoting evidence-based recommendations becomes standard practice, these treatments will not enter future guideline development without new data supporting efficacy and insurance companies may not support their use. This in turn could result in reliance on newer, more costly medications with higher-quality data, effectively increasing the cost of caring for patients with hypersomnia conditions.

The TF encourages the field to identify validated outcome measures that most closely reflect patient priorities, to develop and validate disease-specific patient-reported outcome measures, and to delineate CSTs to harmonize future research and facilitate future clinical guideline creation. Additional research focused on quality-of-life measures, both cross-sectional and longitudinal, will also help the field better understand aspects of the disease most disruptive to patient lifestyles. Use of standardized, validated assessments will also permit clinicians and patients to compare clinical trial data to get a rough estimate of comparative effectiveness.

Continued research is also necessary to understand the mechanisms of hypersomnia and excessive daytime sleepiness in specific conditions, so that more targeted therapies can be developed. For instance, understanding the role of the innate and adaptive immune system in the development of narcolepsy should herald clinical trials in immune-modulating treatments that could attenuate disease severity. Likewise, revelation of the molecular architecture of the human orexin receptor[129] should aid efforts for development and testing of orexin-specific therapies. It is the TF's hope that mechanistic data for understudied conditions like Kleine-Levin syndrome, idiopathic hypersomnia, NT2, and hypersomnia due to specific medical and psychiatric disorders will also lead to targeted drug development and testing.

Many central disorders of hypersomnolence start in childhood and adolescence, yet clinical trials of medications are lacking for those under age 18 years. Because children and adolescents may react differently to these medications than adults, and side effect profiles can vary based on patient age, high-quality RCTs are needed for pediatric patients with CNS hypersomnia. Our collective hope is that the next time this guideline is updated, pediatric-specific data will allow for robust clinical recommendations focused on this unique population.

Finally, reliance on medications alone to treat CNS hypersomnia conditions is likely insufficient without broader guidance on behavioral and environmental influences on symptom management. Cognitive-behavioral therapy (in-person, online), sleep scheduling, naps, exercise, and specific diets may further medication effects and could hold independent treatment benefit, and thus deserve further study.

SUMMARY

CNS hypersomnia disorders are among the most devastating sleep disorders because of the functional limitations and safety risks they cause. This analysis offers a comprehensive evaluation of available evidence for CNS hypersomnia therapies using GRADE. While the TF intends this analysis to be a useful guide for health care providers in discussing and recommending treatments for patients with CNS hypersomnia, it also highlights the areas in which data are still insufficient for evidence-based decision-making. Despite some limitations, however, patients and health care providers should be encouraged that treatments for CNS hypersomnia conditions have expanded from the last iteration of these practice guidelines. The ongoing efforts of researchers to develop and test new medications for these disorders are promising. Continued funding for research underlying the etiology of these conditions is necessary so that more targeted and effective treatments can be developed. Systematic outcome measures that incorporate patient values need to be employed across clinical trials to allow for future treatment meta-analyses. At the same time, research on nonpharmacological management of symptoms is needed to further bolster disease management and cope with chronic symptoms. Collaborations between patient groups, health care providers, researchers, government funding agencies, and industry will be necessary to spur treatment progress.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
ADD, attention-deficit disorder
ADHD, attention-deficit hyperactivity disorder
AE, adverse event
AHI, apnea-hypopnea index
BFI, Brief Fatigue Inventory
BOD, Board of Directors
CGI, Clinical Global Impression
CGI-C, Clinical Global Impression of change
CGI-EDS, Clinical Global Impression-excessive daytime sleepiness
CGI-S, Clinical Global Impression scale for sleepiness
CI, confidence interval
CME, continuing medical education
CMS, Centers for Medicare & Medicaid Services
CNS, central nervous system
COI, conflict of interest
CPM, Canadian Product Monograph
CST, clinical significance threshold
DLB, dementia with Lewy bodies
EDS, excessive daytime sleepiness
ER, extended-release
ESS, Epworth Sleepiness Scale
FDA, U.S. Food & Drug Administration

FOSQ, Functional Outcomes of Sleep Questionnaire
FSS, Fatigue Severity Scale
GHB, gamma hydroxybutyrate
GIR, Global Improvement Rating
GRADE, Grading of Recommendations, Assessment, Development and Evaluation
ICSD, *International Classification of Sleep Disorders*
IPA, Inernational Pharmaceutical Abstracts
IQR, interquartile ratio
IV, intravenous
IVIG, intravenous immune globulin
JESS, Japanese Epworth Sleepiness Scale
MAO-I, monoamine oxidase inhibitor
MDD, major depressive disorder
MSLT, Multiple Sleep Latency Test
MWT, maintenance of wakefulness test
NADAC, National Average Drug Acquisition Cost
NT1, narcolepsy type 1
NT2, narcolepsy type 2
PGI-C, Patient Global Impression of Change
PI, principal investigator
PICO, patient population, intervention, comparison, and outcomes
PRO, patient-reported outcome
PSQI, Pittsburgh Sleep Quality Index
PVT, psychomotor vigilance task
RCT, randomized controlled trial
REMS, risk evaluation mitigation strategy
RRT, reciprocal of the reaction time
SAD, seasonal affective disorder
SD, standard deviation
SE, standard error
SEK, Swedish Krona
SF-36, 36-Item Short-Form Health Survey
SMD, standardized mean difference
SNRI, serotonin/norepinephrine reuptake inhibitor
SSRI, selective serotonin reuptake inhibitor
SSS, Stanford Sleepiness Scale
TBI, traumatic brain injury
TF, task force
type 2 DM, type 2 diabetes mellitus

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ACKNOWLEDGMENTS

The task force thanks and acknowledges the early contributions of Todd Swick, MD; Jonathan Heald, MA; and Vanessa Gonzalez, MPH. Mr. Heald was the former director of the Science and Research Department at the AASM; and Ms. Gonzalez was the staff for the initial phase of the project. The task force also thanks Lois Krahn, MD, and Emmanuel Mignot, MD, PhD, for serving as external reviewers of the document and providing valuable feedback.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication 16 April, 2021
Submitted in final revised form 16 April2021
Accepted for publication 16 April, 2021
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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The development of this paper was funded by the American Academy of Sleep Medicine (AASM). Dr. Rowley and Dr. Trotti serve on the AASM Board of Directors. Ms. Hashmi is employed by the AASM. Dr. Maski has research funding from the National Institute of Neurological Disorders and Stroke (K23 NS104267-01A1) and a Jazz Pharmaceuticals investigator-initiated grant, and she was a site PI for a pediatric narcolepsy sodium oxybate clinical trial sponsored by Jazz Pharmaceuticals. She has been a consultant for Harmony Biosciences (March 2018–March 2019), Jazz Pharmaceuticals (June 2017–August 2020 and January 2021), Roche Pharmaceuticals (November 2017), and Alkermes (May 2020 and January 2021). She was a speaker for a CME program funded by Harmony Biosciences entitled "Patient, Provider, and Caregiver Connection: A Patient's Journey Living with Narcolepsy" on February 23, 2021. Due to her conflicts, Dr. Maski did not participate in developing or voting on final recommendations for sodium oxybate, solriamfetol, and pitolisant. Dr. Watson was a consultant for Harmony Biosciences (September 2018–December 2020) and Jazz Pharmaceuticals (October 2018–April 2019). Dr. Trotti has research funding from the AASM Foundation and is a PI for the National Institute of Neurological Disorders (R01 NS111280). Dr. Swick is employed full-time by Takeda Pharmaceuticals as a Senior Medical Director for their neuroscience's clinical division (September 2019-present). Dr. Swick resigned from the task force in September 2019 due to this conflict, which was after completion of the initial draft of this systematic review. After resigning from the task force, Dr. Swick did not participate in any further development or editing of this manuscript and is listed as an author for the contributions he made prior to taking on the conflict. Dr. Swick also served as a paid speaker for Jazz Pharmaceuticals (January 2012-January 2019), received research funding from Balance Therapeutics (January 2019-August 2019), Jazz Pharmaceuticals (September 1999-September 2019), and Avadel/Flamel Technologies (March 2016-September 2019). The other authors do not report any conflicts of interest.