Treatment of Central Disorders of Hypersomnolence: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment

**Introduction**: This systematic review provides supporting evidence for the accompanying clinical practice guideline on the treatment of central disorders of hypersomnolence in adults and pediatric populations. The review focuses on prescription medications with United States Food and Drug Administration (FDA) approval and non-pharmacologic 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 non-pharmacological 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 698 studies; 142 are included in this review. Evidence for the following interventions are 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.

**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. As classified in the International Classification of Sleep Disorders, 3rd edition (ICSD-3), 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 United States Food and Drug Administration (FDA) approved prescription medications and non-pharmacologic 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. Subsequent advances in sleep medicine, including the publication of the International Classification of Sleep Disorders as well as the worldwide growth of professional sleep societies, have resulted in 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 (e.g. obstructive sleep apnea), insufficient sleep and/or circadian dysrhythmias. The presence of hypersomnia 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 irresistible need to sleep or daytime elapses into sleep. Diagnostic criteria of all CNS hypersomnia conditions 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 (ICSD, 3rd edition) and characteristic symptoms are reviewed below.

NT1 is characterized by the presence of cataplexy and defined pathophysiology by 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 (subjectively defined by frequent waking periods during the night) also commonly occurs in narcolepsy, especially NT1. Cataplexy functional impact varies between NT1 patients 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 their daily functions are more impaired by general symptoms of fatigue and cognitive difficulties. 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 non-restorative sleep (despite high sleep efficiency on a nocturnal polysomnography), prolonged and severe sleep inertia, long sleep durations, and impaired daytime cognitive functions on a near daily basis. Kleine-Levin syndrome patients 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 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.

If pathologic sleepiness is determined to be a direct result of an underlying medical or neurological condition, 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 auto-immune 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 hypersomnia, impairments in alertness predispose individuals to serious decrements in performance and function. Consequently, patients’ symptoms can significantly impact quality of life, 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.

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. When these directives were updated in 2001, evidence-based guidelines were based on growing clinical trial data and reporting of adverse events. (adapted from Sackett) The practice parameters favored the recently arrived 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. The 2001 practice guideline also highlighted possible treatments for another important symptom of narcolepsy, cataplexy, with specific mention of tricyclic antidepressants and fluoxetine.

A similar evidence-based assessment was utilized in the 2007 practice parameters. 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.

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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 anti-cataplectic 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 hypsomnolence remained unchanged and modafinil was additionally recommended based upon one publication.

The present document serves as the most recent AASM systematic review regarding the treatment of central disorders of hypsomnolence. Perhaps the biggest change in comparison to previous versions is use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system of evidence analysis. 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, many previously recommended interventions may be negated or left inconclusive using GRADE, leaving some questions unanswered. While this certainly points out significant gaps in current clinical research pertaining to central disorders of hypsomnolence, these updated recommendations are intended to provide clinicians with heightened confidence in prescribing reviewed treatments and serve as a roadmap for future clinical trials that will provide an even more robust evidence base.

**METHODOLOGY**

**Expert Task Force**

The AASM commissioned a task force (TF) comprised of board-certified sleep medicine specialists who are experts in the treatment of central disorders of hypsomnolence. 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 section.

**PICO Questions**

PICO (Patient population, Intervention, Comparison, and Outcomes) questions were developed by the TF based on a review of the existing AASM practice parameters on the treatment of central disorders of hypsomnolence 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 healthcare 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 TF literature review of commonly used thresholds for the various tools, gathering input from other sleep specialists, clinical judgment, and experience.

Table 1 - PICO Questions

| 1 | **Population:** Adult and pediatric patients diagnosed with Narcolepsy Type 1 or 2  
**Intervention:** Pharmacological therapy: Anti-Parkinson Agent (Amantadine), Benzodiazepine receptor agonists (Eszopiclone, Zaleplon, Zolpidem), Benzodiazepine receptor antagonist (Flumazenil), Benzodiazepine (Temazepam, Triazolam), Central Nervous System Depressant (Sodium oxybate), Central Nervous System Stimulant (Amphetamines and related preparations, Ammodafinil, 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 (Amtriptyline, Amoxapine, Clomipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Trimipramine), Combination therapy, light therapy and norepinephrine and dopamine reuptake inhibitor, 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 Agent (Amantadine), Benzodiazepine receptor agonists (Eszopiclone, Zaleplon, Zolpidem), Benzodiazepine receptor antagonist (Flumazenil), Benzodiazepine (Temazepam, Triazolam), Central Nervous System Depressant (Sodium oxybate), Central Nervous System Stimulant (Amphetamines and related preparations, Ammodafinil, 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 (Amtriptyline, Amoxapine, Clomipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Trimipramine), Combination therapy, light therapy and norepinephrine and dopamine reuptake inhibitor, 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), Antimanic Agent (Lithium Carbonate), Anti-Parkinson Agent (Amantadine), Antipsychotic (Risperidone), Benzodiazepine receptor antagonist (Flumazenil), Central Nervous System Stimulant (Amphetamines and related preparations, Ammodafinil, 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), light therapy and norepinephrine and dopamine reuptake inhibitor, 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

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 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), Combination therapy, light therapy and norepinephrine and dopamine reuptake inhibitor, 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Narcolepsy</td>
</tr>
<tr>
<td>Accident risk</td>
<td>√*</td>
</tr>
<tr>
<td>Cataplexy</td>
<td>√*</td>
</tr>
<tr>
<td>Cognitive performance</td>
<td></td>
</tr>
<tr>
<td>Difficulty waking in the morning</td>
<td>√*</td>
</tr>
<tr>
<td>Disease severity</td>
<td>√*</td>
</tr>
<tr>
<td>Excessive daytime sleepiness (EDS)</td>
<td>√*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>√</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
</tr>
<tr>
<td>Quality of life</td>
<td>√*</td>
</tr>
<tr>
<td>Sleep inertia</td>
<td></td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>√</td>
</tr>
<tr>
<td>Work/school performance/attendance</td>
<td>√*</td>
</tr>
</tbody>
</table>

*Critical outcomes

Table 3 – Summary of Clinical Significance Thresholds for Critical and Important Outcome Measures

<table>
<thead>
<tr>
<th>Outcome Tool</th>
<th>Clinical Significance Threshold*</th>
<th>Desired change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accident risk</td>
<td>10%</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Cataplexy</strong></td>
<td></td>
<td></td>
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<tr>
<td>--------------------</td>
<td>-----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Daily/weekly episode frequency</td>
<td>25%</td>
<td>Decrease</td>
</tr>
<tr>
<td>Severity</td>
<td>25%</td>
<td>Decrease</td>
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<table>
<thead>
<tr>
<th><strong>Cognitive performance</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor vigilance test- Reciprocal reaction time</td>
<td>10%</td>
<td>Increase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Difficulty waking in the morning</strong></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Varies</td>
<td>0.5 SMD</td>
<td>Decrease</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Disease severity</strong></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>CGI</td>
<td>1 point OR</td>
<td>Decrease</td>
</tr>
<tr>
<td>PGI</td>
<td>1 point OR</td>
<td>Improvement</td>
</tr>
<tr>
<td>Frequency and duration of symptoms</td>
<td>10%</td>
<td>Decrease</td>
</tr>
<tr>
<td>Number of days incapacitated</td>
<td>10%</td>
<td>Decrease</td>
</tr>
<tr>
<td>Other quantitative tools</td>
<td>10%</td>
<td>Improvement</td>
</tr>
<tr>
<td>Other qualitative tools</td>
<td>33% of patients reporting change</td>
<td>Improvement</td>
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<table>
<thead>
<tr>
<th><strong>Excessive daytime sleepiness</strong></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>ESS</td>
<td>2 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>ESS (CHAD)</td>
<td>2 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>MWT</td>
<td>2 minutes</td>
<td>Increase</td>
</tr>
<tr>
<td>MSLT</td>
<td>1 minute</td>
<td>Increase</td>
</tr>
<tr>
<td>SSS</td>
<td>1 point</td>
<td>Decrease</td>
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<table>
<thead>
<tr>
<th><strong>Fatigue</strong></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>FSS (global change)</td>
<td>0.5 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>SF-36 Energy/Vitality sub scale</td>
<td>3 points</td>
<td>Increase</td>
</tr>
<tr>
<td>BFI</td>
<td>0.3 points</td>
<td>Increase</td>
</tr>
<tr>
<td>FIS</td>
<td>4.8 points</td>
<td>Increase</td>
</tr>
<tr>
<td>MAF (global change)</td>
<td>5.0 points</td>
<td>Increase</td>
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<tr>
<th><strong>Mood</strong></th>
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<tbody>
<tr>
<td>BDI</td>
<td>5 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>CDI</td>
<td>6 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>PHQ-2</td>
<td>1 point</td>
<td>Decrease</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>2 points</td>
<td>Decrease</td>
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<table>
<thead>
<tr>
<th><strong>Work/ school performance/ attendance</strong></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Varies</td>
<td>0.5 SMD</td>
<td>Increase</td>
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<table>
<thead>
<tr>
<th><strong>Quality of Life</strong></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>FOSQ</td>
<td>1 point</td>
<td>Increase</td>
</tr>
<tr>
<td>PedsQL</td>
<td>1 point</td>
<td>Increase</td>
</tr>
<tr>
<td>SF-36</td>
<td>3 points</td>
<td>Increase</td>
</tr>
<tr>
<td>(Physical Component Summary)</td>
<td>---</td>
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</tr>
<tr>
<td>SF-12</td>
<td>3 points</td>
<td>Increase</td>
</tr>
<tr>
<td>(Mental Component Summary)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>SF-12</td>
<td>4 points</td>
<td>Increase</td>
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<table>
<thead>
<tr>
<th><strong>Sleep Inertia</strong></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Varies</td>
<td>0.5 SMD</td>
<td>Decrease</td>
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<table>
<thead>
<tr>
<th><strong>Sleep Quality</strong></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>PSQI</td>
<td>3 points</td>
<td>Decrease</td>
</tr>
<tr>
<td>PSGI/Actigraphy based Sleep Efficiency (%)</td>
<td>10%</td>
<td>Increase</td>
</tr>
</tbody>
</table>

*The clinical significance threshold applies to the comparison of post-treatment 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 score; ESS-CHAD - Epworth Sleepiness Scale for Children and Adolescents; FSS - Fatigue
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. A final literature search was performed in February 2020. 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 20 additional articles by doing a spot check for a total of 698 articles that were screened for inclusion/exclusion in the guideline.

The TF set inclusion and exclusion criteria, which are presented in the supplemental material and summarized in Figure 1. All abstracts were reviewed based on inclusion/exclusion criteria by two TF members. Any discrepancies between the reviewers were discussed and resolved by the Chair or Vice-Chair. A total of 142 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. The pooled results for each continuous outcome measure are expressed as the mean difference between the intervention and comparator. Data from baseline and last-treatment time points from non-randomized trials were also compared. These are presented in a table format in 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 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. If outcome data were not presented in the format necessary for statistical analysis (i.e., mean, standard deviation, and sample size), or data were presented only in graphical formats, the authors 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, the paper was included in the evidence base as supporting evidence and the data were estimated and presented in a table in supplemental material. These data were not used for meta-analysis nor for determining 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 risk difference. The risk difference is defined as the difference between the observed risks (proportions of individuals with the outcome of interest) in the two 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 four individual GRADE domains: quality of evidence, balance of beneficial and harmful effects, patient values and preferences, and resource use.  

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 (I² 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 hypersomnia would see. The TF determined overall quality of the evidence for a given treatment based on strength of evidence for all critical outcomes, relying exclusively on RCT data when available. Important outcomes are not considered when determining the overall quality of evidence.

2. **Benefits versus 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 was 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. For some drugs, unit pricing was 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 covered outpatient drugs. Data is calculated by the Centers for Medicare and 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).  

**Public Comment and Final Approval**

Drafts of the systematic review and accompanying guideline were made available for public comment for a two-week period on the AASM website. AASM members, the general public 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 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 addressing the treatment of narcolepsy. 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 one randomized, double-blind, placebo-controlled trial and one open label flexible dose study 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.

An open label study assessed armodafinil doses of 100-250 mg in 50 patients with unspecified narcolepsy.

The figures and tables are provided in the supplemental material, Figure S1 and Tables S1-S5. A summary of findings table is provided in the supplemental material, Table S6. 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:** The RCT 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) demonstrated a clinically significant pre-post difference in the mean ESS score of 4.7 points lower (95% CI: 1.93 to 7.41 minutes lower) in patients with narcolepsy (type 1 or 2). Quality of evidence was very low due to imprecision. (see supplemental material, Table S1)

The RCT assessed improvement in objective sleepiness using the Maintenance of Wakefulness Test (MWT). The mean change from baseline in the MWT score in the armodafinil group was an estimated 3.31 minutes higher (95% CI: 1.12 min to 5.50 min higher) compared to placebo. Quality of evidence was moderate. (see supplemental material, Table S2)

**CATAPLEXY:** The RCT reported on the incidence of self-reported daily cataplexy episodes between any of the armodafinil dose groups and placebo as 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:** The RCT 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%, compared with 33%
for placebo. There was a clinically significant improvement of 38% noted in the armodafinil group. Quality of evidence was high. (see supplemental material, Table S3)

**ACCIDENT RISK**: The RCT\(^2\)\(^1\) reported on diary based mean reduction in number of patients who reported mistakes, near misses, and accidents. There was a clinically significant mean reduction of 26.5% between armodafinil compared to placebo. The quality of evidence was moderate and was downgraded due to imprecision. (see supplemental material, 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**: The RCT utilized the 9-item Brief Fatigue Inventory (BFI) to assess change in fatigue levels. \(^2\)\(^1\) The mean BFI score in the armodafinil group was clinically significant at 1.10 points lower (95% CI: 0.48 to 1.72 points lower) compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S1)

**SLEEP QUALITY**: The RCT\(^2\)\(^1\) reported on the change in sleep quality on the basis of sleep efficiency assessed by polysomnography. There was an insignificant improvement in sleep efficiency of 2.5% (95% CI: 6.28% higher to 1.28 lower) in the armodafinil group when compared to placebo. Quality of evidence was high. (see supplemental material, 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 RCT and downgrading of the quality of evidence because of imprecision. \(^2\)\(^1\)

**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. \(^2\)\(^1\) Adverse events leading to withdrawal occurred in seven narcolepsy patients and consisted of ‘urticaria with angioedema’ and ‘urticaria with sleep disorder’, 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 0.11 (95% CI: 0.01 to 0.22) indicating greater risk of headache with armodafinil use. (see supplemental material, Figure S65) Other commonly reported adverse events in armodafinil group in the RCTs included nausea (10.7%), upper respiratory tract infection (9%) and dizziness (8.4%). Commonly reported adverse events across all observational studies on the use of armodafinil include headache (24.2%), sinusitis (10.2%), somnolence (10.2%), anxiety (8.1%), nausea (8.1%) and nasopharyngitis (8.1%). The more serious but rare AEs reported in product information for armodafinil, such as Stevens Johnsons 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 studies, fetal developmental toxicity was observed at clinically relevant exposures. While armodafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. \(^2\)\(^3\) Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy.

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*Version. 15JUNE 2020*
**Resource Use**
Per the NADAC database, the unit cost of 50 and 250 mg tablets ranged from $0.26 to $1.18. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 non-pregnant patients would probably use armodafinil when compared to no treatment for their narcolepsy. The side-effect profile is better than traditional stimulants, including a lower risk of cardiovascular disease or abuse potential.

**Clomipramine**
TF review of the literature identified a single retrospective observational long-term self-reported study in 16 subjects with NT1 on clomipramine alone (dosage range 25-125 mg; mean dosage 49 mg/24hrs.). The data table is provided in the supplemental material, Table S7. A summary of findings table is provided in the supplemental material, Table S8. 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. The mean pre-post difference in ESS in adult patients on clomipramine was clinically significant at 3.2 points lower (95% CI: 0.07 points to 6.33 points lower). The quality of evidence was very low due to imprecision. (see supplemental material, 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 treatment of narcolepsy was very low, based on the critical outcome reported in the study and downgrading of the quality of evidence because of imprecision.

**Benefits and Harms**
The TF concluded that the overall balance between the desirable effect on excessive daytime sleepiness and undesirable effects probably did not favor the use of clomipramine.

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

There are no adequate or well-controlled studies in pregnant women. Clomipramine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 mg – 50 mg doses ranged from is $3.49- $3.41 for each capsule. Medication cost to any given patient is uncertain and are determined by insurance coverage, co-pays, and deductibles.

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

Dextroamphetamine
The TF identified three studies focused on dextroamphetamine in their literature review. 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. Another one was an observational, single blind study assessing the effect of dexamphetamine sulphate (10 and 30 mg/day) and dexamphetamine spansules (10 mg) in 20 patients with NT1 and NT2 over a 4-week period. The third study was a single retrospective observational long-term self-reported study case series investigating episodes of sleepiness and cataplexy in 60 subjects with NT1 on dexamphetamine alone (dosage range 5-60 mg; mean dosage 16 mg/24/hr.).

The data tables are provided in the supplemental material, Tables S9-S10. A summary of findings table is provided in the supplemental material, Table S11. 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 unspecified narcolepsy patients on dextroamphetamine using the ESS score. It demonstrated a clinically significant pre-post difference in the mean ESS score of 5.0 points lower (95% CI: 3.43 points to 6.57 points lower). The quality of evidence was determined to be very low due to imprecision. (see supplemental material, Table S9)

**CATAPLEXY:** One observational single blind study reported on changes in daily cataplexy episode rate in patients with unspecified narcolepsy. 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 supplemental material, 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 concluded that the overall quality of evidence for dextroamphetamine for the treatment of narcolepsy was very low based on the critical outcomes reported in the two studies and downgrading of the quality of evidence because of imprecision.

Benefits and Harms
The TF concluded that the balance between the desirable and undesirable effects is 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 sweating (25%) and feeling ‘on the edge’ (30%). 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.

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

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. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic 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.

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 mg – 15 mg doses ranged from $1.40- $1.80 for each unit. Costs are likely to vary and are determined by insurance coverage, co-pays, 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, cross-over and placebo-controlled trial of L-carnitine (510 mg/day) of 16 weeks’ duration in 28 subjects with NT1.

The data figures are provided in the supplemental material, Figures S2-S4. A summary of findings table is provided in the supplemental material, Table S12. 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: The RCT reported on changes in sleepiness scores using the Japanese Epworth Sleepiness Scale (JESS). The mean JESS score in the L-Carnitine group was not clinically significant at 0.0 points higher (95% CI: 1.96 lower to 1.96 points higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S2)

Cataplexy: The RCT reported on changes in daily cataplexy rates. Data reported were not suitable for analysis.

Quality of Life: The 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 was not clinically significant at 0.50 points higher (95% CI: 3.46 points higher to 3.46 points lower) compared to placebo. Quality of evidence was moderate due to imprecision. (see supplemental material, 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:** The RCT reported on fatigue using the vitality sub-scale of the SF-36. The mean SF-36 energy/vitality component score in the L-Carnitine group was 2.0 points higher (95% CI: 7.5 points higher to 3.5 points lower) compared to placebo. This result was not clinically significant. Quality of evidence was moderate due to imprecision. (see supplemental material, 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 RCT and downgrading of the quality of evidence because of imprecision.

**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 insignificant clinical effect on sleepiness in patients with NT1. However, L-carnitine was well tolerated with no side effects observed. 29

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

**Resource Use**
This medication is available over the counter as a non-pharmacologic 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 one observational prospective cohort study examining the efficacy of methylphenidate (mean dose 43 mg) in the treatment of unspecified narcolepsy in 11 patients.30

The TF also identified one case series of 106 unspecified narcolepsy patients, ranging from 22 yrs.- 64 yrs. treated with 10-60 mg of methylphenidate.31

The data tables are provided in the supplemental material, Table S13. A summary of findings table is provided in the supplemental material, Table S14. 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:** The prospective cohort reported on the ability to maintain wakefulness in patients with unspecified narcolepsy on methylphenidate.30 The mean MWT post-treatment score in the methylphenidate group was 18.4 minutes. Data reported were not suitable for analysis.

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Disease Severity: The study reported on improvement in disease severity using the Global Improvement Rating (GIR) scale. As the mean daily dose of methylphenidate was increased from 10 to 60 mg, moderate or marked improvement on the GIR was noted in 89.7% of the patients, which was clinically significant. Quality of evidence is very low. (see supplemental material, Table S13)

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 the overall quality of evidence for methylphenidate for the treatment of narcolepsy was very low based on the critical outcome reported and downgrading the quality of evidence because of imprecision.

Benefits and Harms
The TF concluded that the balance between the desirable and undesirable effects is 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%). 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%).

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. There are no adequate or well-controlled studies in pregnant women. Methylphenidate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised if administered to nursing mothers.

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 mg-20 mg], and $1.95-3.51/capsule [10 mg-60 mg]. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 two RCTs assessing the efficacy of modafinil treatment for adult patients with NT1 compared to placebo and one observational study of modafinil efficacy among adult NT1 patients. Sample sizes ranged from 19 to 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 eight RCTs for the treatment of unspecified narcolepsy with modafinil vs. placebo. 36-43 Four observational studies of modafinil use in patients with unspecified narcolepsy with sample sizes ranging from 38 to 471 and study durations ranging from 5-40 weeks. 44-47

The meta-analyses and figures and tables are provided in the supplemental material, Figures S5-S12 and Tables S15-S22. A summary of findings table is provided in the supplemental material, Table S23. 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 ESS for adult patients with NT1. 34 The study demonstrated a clinically significant difference of 10.30 points lower (95% CI: 7.95 to 12.65 points lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S5)

One observational study assessed the effects of modafinil on excessive daytime sleepiness in patients with NT1 using the ESS. 35 The mean ESS score range of pre-post differences on modafinil was a clinically significant 2.20 points lower (95% CI: 0.85 to 3.55 points lower), supporting the findings of the RCT. The quality of evidence was very low due to imprecision. (see supplemental material, Table S15)

Five RCTs and two cross-over trials evaluated the effect of modafinil on excessive daytime sleepiness for the treatment of unspecified narcolepsy using the ESS. 36-40, 42, 43 Doses ranged from 200-600 mg/day. The meta-analyses demonstrated a clinically significant reduction of 2.77 points (95% CI: 1.73 to 3.80 lower) when compared to placebo. The quality of evidence was high. (see supplemental material, Figure S6)

In addition, three observational studies of modafinil assessed the effects of modafinil on excessive daytime sleepiness among patients with unspecified narcolepsy using the ESS. 45, 47, 48 Pre-post difference results could only be reported for two of the studies 45, 48 because the third study 37 did not report pre-modafinil treatment parameters. The mean ESS score pre-post difference in these patients ranged from 0.92 to 4.10 points lower. The quality of evidence was very low due to imprecision. (see supplemental material, Table S16)

Five RCTs and two crossover trials evaluated the effect of modafinil on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT. 36-40, 42, 43 The mean MWT score in the modafinil group was a clinically significant 4.14 minutes higher (95% CI: 3.44 min to 4.84 min higher) compared to placebo. The quality of evidence was high. (see supplemental material, 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. 33 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 2.09 minutes higher (95% CI: 0.42 min lower to 4.60 min higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Table S17)

The TF identified two RCTs that compared the effect of modafinil to placebo for assessment of sleepiness by using the MSLT in patients with unspecified narcolepsy. 42, 43 The mean MSLT score in patients on modafinil was 1.58 minutes higher (95% CI: 0.92 min to 2.24 mins higher) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S8)

**Cataplexy:** One RCT reported on daily cataplexy episodes in patients with unspecified narcolepsy 37 though patients presumably had NT1. The % difference in cataplexy reduction was 25% which is clinically significant. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Table S18)

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Another RCT reported on daily cataplexy episodes in patients with NT1 on modafinil. There were no baseline data on the daily cataplexy episodes and so it was not feasible to calculate the % reduction. The study mentions 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). It demonstrated a clinically insignificant mean difference of 0.29 points lower (95% CI: 3.40 points lower and 2.82 points higher) The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S9)

Three RCTs evaluated disease severity in adult patients with unspecified narcolepsy as measured by the CGI. The percentage of patients reporting an improvement ranged from 19% to 72% in the modafinil group compared to placebo. In addition, one of the RCTs reported the subjects randomized to modafinil treatment had an 86% improvement in CGI-EDS over placebo. All CGI results met the threshold for clinical significance. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Table S19)

**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. The physical health summary component demonstrated an insignificant 0.5 points higher (95% CI: 2.23 points higher to 1.23 points lower) compared to placebo. The quality of evidence was high. (see supplemental material, Figure S10)

The mental health summary component demonstrated a clinically significant mean difference of 3.49 points higher (95% CI: 1.76 points to 5.22 points higher). The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S10)

Two observational studies to assess treatment efficacy with modafinil vs placebo in patients with unspecified narcolepsy showed greater benefit of modafinil on the mental health domain compared to the physical health domain on the SF-36. The mean SF-36 physical health summary component pre-post difference ranged from 1.3 to 2.3 points higher. The quality of evidence was low. (see supplemental material, Table S20)

The mean SF-36 mental health summary component pre-post difference ranged from 3.0 to 4.40 points higher. The quality of evidence was low. (see supplemental material, Table S21)

**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. The mean SF-36-energy and vitality component in the modafinil group demonstrated a clinically significant 7.98 points higher (4.31 to 11.65 points higher) compared to placebo. The quality of evidence was high. (see supplemental material, Figure S11)

Two observational studies also showed benefit on the SF-36 vitality score in patients with unspecified narcolepsy. They demonstrated a pre-post difference range of 13.0 to 19.50 points higher. The quality of evidence was low. (see supplemental material, Table S22)

**Sleep Quality:** One RCT reported on sleep quality in a post hoc analysis 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’. 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 RCTs and downgrading of the quality of evidence because of imprecision.

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, 0.08), anxiety or nervousness: 0.03 (95% CI: -0.01, 0.06) and dry mouth: -0.02 (95% CI: -0.07, 0.12).

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: 0.04, -0.02), 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 (95% CI: -0.02 to 0.07). 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%). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.23 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 mg – 200 mg doses ranged from is $0.92 to 1.02 for each tablet. 24 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 non-pregnant 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
The TF literature review identified one observational study that investigated the effectiveness of nap therapy for adult patients with narcolepsy.50 Sixteen patients with unspecified narcolepsy were enrolled in a month-long program of three regularly scheduled 15-minute naps.

The figures and tables are provided in the supplemental material, Table S24. A summary of findings table is provided in the supplemental material, Table S25. 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. The mean MWT pre-post difference in the naps group was 2.60 minutes higher (95% CI: 6.69 minutes higher to 1.49 minutes lower). This was a clinically significant change. The quality of evidence was downgraded to very low due to imprecision. (see supplemental material, 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. The study identified in our literature review did not report data for fatigue or sleep quality.

**Overall Quality of Evidence**
Based on available data, the TF determined that the quality of evidence for the treatment of excessive daytime sleepiness with naps alone is very low and downgrading of the quality of evidence because of imprecision.

**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 cost.

**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 their work/school schedules and work/school-place environment.

**Pitolisant**
The TF identified one 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. 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 five 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. The literature search also identified one placebo controlled cross-over study of 22 patients with NT1 treated with 40 mg of tiprolisant (former name for pitolisant).

All three studies were industry funded. Data for outcomes - Epworth Sleepiness Scale scores, the MWT, rates of cataplexy and the CGI-C Cataplexy from 2 studies were obtained from personal communication via email correspondence with Craig Davis, Psy.D., Sr. Medical Director Medical Affairs, Harmony Biosciences, LLC in June 2019. Details of data obtained from this communication are included in the supplemental material.
The figures and tables are provided in the supplemental material, Figures, S12-S17 and Tables S26-S27. A summary of findings table is provided in the supplemental material, Table S28. 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.51,52 Meta-analysis showed a clinically significant improvement of 3.75 points lower (95% CI: 2.04 points to 5.46 lower) compared to placebo. The quality of evidence was high. (see supplemental material, Figure S12)

Another RCT evaluated the effect of pitolisant on excessive daytime sleepiness in patients with unspecified narcolepsy using the ESS.37 The mean ESS score in the pitolisant group demonstrated a clinically significant reduction of 3.6 points (95% CI: 0.93 to 6.27 points lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S13)

One RCT (n=61) evaluated the effect of pitolisant on the ability to maintain wakefulness in patients with unspecified narcolepsy using MWT.37 There was a clinically significant mean MWT score of 2.10 minutes higher (95% CI: 0.64 to 3.65 minutes higher) in the pitolisant group compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S14)

Another RCT evaluated the effect of pitolisant on the ability to maintain wakefulness in patients with NT1 using the MWT.51 The mean MWT score in the pitolisant group was clinically significant 4.3 minutes higher (95% CI: 9.05 minutes higher to 0.45 minutes lower) compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S15)

**Cataplexy:** One RCT37 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 56.06% reduction. The quality of evidence was moderate due to imprecision. (see supplemental material, Table S26)

Another RCT evaluated the change in weekly cataplexy episodes in patients with NT1.51 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 37.03% reduction. The quality of evidence was high. (see supplemental material, Table S27)

**Disease Severity:** One RCT evaluated the disease severity using the (CGI-C) on cataplexy in patients with unspecified narcolepsy.37 The mean CGI-C score in the pitolisant group was a clinically insignificant 0.5 points lower (95% CI: 1.3 points lower to 0.3 points higher) when compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S16)

Another RCT evaluated disease severity using the same tool as above in patients with NT1.51 The mean CGI-C score in the pitolisant group was not clinically significant at 0.9 points lower (95% CI: 1.33 to 0.47 points lower) when compared to placebo. Quality of evidence was high. (see supplemental material, Figure S17)

**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 was considered high based on the critical outcomes reported in the RCTs. Clinical significance thresholds were met for sleepiness as defined by the ESS, MWT and for subjective cataplexy frequency.

**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 for headache between pitolisant and placebo was 0.05 (95% CI: -0.11 to 0.21). Other commonly reported adverse events included abdominal discomfort (6%), nausea (6%), diarrhea (3%) and dizziness (3%). The majority (95%) of adverse events occurred during the first 3 days of treatment. None of them resulted in treatment cessation.

Across all RCTs included in the systematic review that reported on the use of pitolisant (irrespective of the indication), the commonly reported adverse events in the pitolisant group included headache (35.4%), insomnia (9.4%), and nausea (7.5%). Four AEs were considered severe: abdominal discomfort, nausea, malaise and insomnia.

Pitolisant has low abuse potential and thus is not a scheduled federally controlled substance. Studies in animals have shown reproductive toxicity, including teratogenicity. 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.

**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 mono-therapeutic aspect of this medication may reduce costs 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, co-pays, 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. Most patients would likely prefer to take a single medication, when possible, to treat their narcolepsy. Medication cost, side-effects, and drug-drug interactions support this approach. Pitolisant provides a monotherapy option for patients with narcolepsy. 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 two double-blind placebo-controlled cross-over studies and one observational prospective cohort study examining the efficacy of selegiline in the treatment of narcolepsy. One study included 17 patients with unspecified narcolepsy and doses of 10, 20, 30, or 40 mg of selegiline over a 4-week period. Another study assessed doses of 10 and 20 mg of selegiline in 30 patients with unspecified narcolepsy and a third study examined 11 patients with unspecified narcolepsy taking 15 to 30 mg of selegiline.

The figure is provided in the supplemental material, Figure, S18. A summary of findings table is provided in the supplemental material, Table S29. 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 1.42 minutes higher (95% CI: 0.11 minutes lower to 2.95 minutes higher) indicating a clinically significant improvement with selegiline. The quality of evidence was rated moderate due to imprecision. (see supplemental material, Figure S18).

An open label study evaluated the effect of selegiline on the ability to maintain wakefulness in patients with narcolepsy using the MWT. The mean MWT post-treatment score in the selegiline group was 9.4 minutes (95% CI: 6.56 to 12.24 minutes). A lack of pre-treatment data prevented the TF to determine clinical significance in improvement on treatment. Quality of evidence was also not assessed.

Cataplexy: A double-blind placebo-controlled cross over study reported on the mean number of weekly cataplexy attacks. 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). 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). 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 the treatment of narcolepsy with selegiline was moderate based on the critical outcome reported in the single RCT and downgrading of the quality of evidence because of imprecision. Clinical significance thresholds were met for objective sleepiness as measured by the MSLT.

Benefits and Harms

The TF determined that the balance between the desirable and undesirable effects was inconclusive. The literature review indicated improved sleepiness in narcolepsy patients 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 two observational studies identified on the use of selegiline included headache (13%) and irritability (5%).

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Finally, selegiline is a monoamine oxidase-B inhibitor and should not be taken with medications that could result in serotonin syndrome (e.g., SSRIs). Adequate data are not available on use of this drug in pregnant women to inform of a drug-related risk. Monoamine oxidase inhibitors (MAO-Is) have considerable risk associated with a black box warning related to suicidal thoughts and behaviors and hypertensive crisis when interacting with many anti-depressant 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. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patient Values and Preferences**
The TF determined 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 which examined the effect of sodium oxybate versus placebo in patients with unspecified narcolepsy, and five RCTs which examined the effect of sodium oxybate in patients with NT1. Sample sizes ranged from 20 to 228. The sodium oxybate dose ranged from 3 and 9 grams.

The TF identified 3 observational studies that examined the effect of sodium oxybate versus placebo in patients with unspecified narcolepsy and 3 studies which examined the effect of sodium oxybate in patients with NT1. The initial dose of sodium oxybate ranged from 3 and 4.5 grams and increased if clinically indicated to a maximum of 9 grams over several weeks.

The meta-analyses and figures and tables are provided in the supplemental material, Figures S19-S24 and Tables S30-S40. A summary of findings table is provided in the supplemental material, Table S41. 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. This study demonstrated a clinically significant reduction of 3.30 points (95% CI: 1.16 points to 5.44 points lower) when compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S19)

Two RCTs evaluated the effect of sodium oxybate on excessive daytime sleepiness in patients with NT1 using the ESS. The meta-analysis showed a clinically insignificant reduction of 1.47 points [0.56 points to 2.38 points lower] when compared to placebo. The quality of evidence was high. (see supplemental material, Figure S20)

One observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with unspecified narcolepsy using the ESS. There was a clinically significant mean ESS pre-post difference score of 5.85 points lower (4.49 to 7.21 points lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S30)

Two observational studies assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with NT1 using the ESS. There was a clinically significant pre-post range reduction in the mean ESS score in patients
on sodium oxybate of 3.8 to 3.9 points lower, supporting the findings of the RCTs. The quality of evidence was very low due to imprecision. (see supplemental material, Table S31)

One RCT compared the effect of sodium oxybate to placebo for assessment of sleepiness by using the MSLT in patients with NT1. 56 The mean MSLT score on sodium oxybate was not clinically significant at 0.70 minutes higher (95% CI: 1.81 min higher to 0.41 mins lower to) compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S21)

One observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in NT1 patients using the MSLT. 65 The mean MSLT score pre-post difference in these patients was a clinically insignificant 0.30 minutes higher (95% CI: 1.91 minutes higher to 1.31 minutes lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S32)

Another observational study assessed the effects of sodium oxybate on excessive daytime sleepiness in patients with unspecified narcolepsy using the MSLT. 62 The mean MSLT score pre-post difference in these patients was a clinically significant 1.52 minutes higher (95% CI: 3.36 minutes higher to 0.32 minutes lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S33)

One RCT evaluated the effect of sodium oxybate on the ability to maintain wakefulness in patients with NT1 using the MWT. 57 The mean MWT score in patients with NT1 on sodium oxybate was clinically significant 3.80 minutes higher (95% CI: 1.16 to 6.44 minutes higher). The quality of evidence was high. (see supplemental material, Figure S22)

One RCT evaluated the effect of sodium oxybate on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT. 40 The mean MWT score in patients with narcolepsy on SO was a clinically significant 5.10 minutes higher [2.47 to 7.73 minutes higher]. The quality of evidence was high. (see supplemental material, Figure S23)

Two observational studies assessed the effects of sodium oxybate on the ability to maintain wakefulness in NT1 patients using the MWT. 62-66 The mean MWT score pre-post difference ranged from 6.1 to 11.9 minutes higher in these patients. The quality of evidence was very low due to imprecision. (see supplemental material, Table S33)

**Cataplexy:** Two RCTs 57, 58 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 supplemental material, Table S34)

An observational study 61 also evaluated weekly cataplexy episodes and reported a pre-post % difference in cataplexy reduction of 86.36% in patients with NT1. This demonstrates a clinically significant reduction. The quality of evidence was very low due to imprecision. (see supplemental material, Table S35)

One RCT 67 evaluated the change in weekly cataplexy episodes two 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 164.38% increase in weekly cataplexy rate following the abrupt cessation of sodium oxybate therapy in these patients when compared with those who continued on sodium oxybate. This increase was clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Table S36)

**Disease Severity:** The CGI-C is a measure of the clinician’s overall impression of change in the patient’s condition. Two RCTs reported on the percentage of patients reporting improvement in CGI scores. 40, 58 This improvement ranged from 48% to 58%. The quality of evidence was high. (see supplemental material, Table S38)

**Quality of Life:** One RCT 60 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 4.80 points higher
(95% CI:1.76 points to 7.84 points higher) compared to placebo, which was clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S24)

The above RCT \(^60\) 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 2.8 points higher (95% CI: 1.44 points lower to 7.04 points higher) compared to placebo. This was not a clinically significant change. The quality of evidence was moderate due to imprecision. (see supplemental material, Table S39)

One RCT \(^68\) 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. \(^60\) The mean SF-36 vitality domain score pre-post difference in patients with NT1 was 5.88 points higher (95% CI: 3.73 points to 8.03 points higher) when compared to placebo. This was a clinically significant change. The quality of evidence was moderate due to imprecision. (see supplemental material, Table S40)

**Sleep Quality:** Two RCTs \(^49, 69\) reported on sleep quality in a post hoc 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 RCTs and downgrading of the quality of evidence because of imprecision. Cataplexy, quality of life, disease severity and daytime sleepiness are improved significantly by sodium oxybate in adult narcolepsy patients.

**Benefits and Harms**

The TF concluded that the balance between the desirable and undesirable effects favor 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 to 0.14), of nausea was 0.10 (95% CI: 0.00 to 0.21), of urinary/renal disturbances was 0.06 (95% CI: 0.01 to 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 to 0.04). 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 for occurrence of a variety of sleep disturbances was 0.10 (95% CI: 0.05 to 0.14), of nausea was 0.10 (95% CI: 0.00 to 0.21), of dizziness was 0.9 (0.04 to 0.14), of urinary/renal disturbances was 0.07 (95% CI: 0.22 to 0.11), of headache was 0.04 (-0.17 to 0.08) and of chest discomfort was 0.02 (0.0 to 0.04). 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%). (see supplemental material, Figures S75-S82)
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. Adequate data are not available on use of this drug in pregnant women. Animal studies have shown no evidence of teratogenicity, but embryolethality was reported. 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.

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 annual estimated cost of Swedish Krona (SEK) 82,927 versus SEK 18,301. 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, co-pays, 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 small risk of AEs for this benefit but acknowledged some patients find twice night dosing to be inconvenient. A balanced discussion between a patient and their clinical provider about the consequences of untreated narcolepsy will be beneficial.

Solriamfetol

The TF literature identified three randomized, double-blind placebo-controlled trials of solriamfetol conducted with patients with unspecified narcolepsy. End points 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 cross-over design of solriamfetol 300 mg goal dose vs. placebo with endpoints measured 2 weeks after treatment initiation. 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 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). Notably both studies had inclusion criteria requiring participants to have a baseline ESS scores ≥ 10 and baseline MWT sleep latencies ≤ 10 min. 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 TONES [Treatment of Obstructive Sleep Apnea and Narcolepsy Excessive Sleepiness] 2 study from the TONES Phase 3 program.

The meta-analyses and figures and tables are provided in the supplemental material, Figures S25-S26 and Tables S42-S44. A summary of findings table is provided in the supplemental material, Table S45. 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, and work/school performance.

Excessive Daytime Sleepiness: Two RCTs evaluated the effect of solriamfetol on excessive daytime sleepiness using the ESS \(^\text{72, 74}\) and showed a clinically significant difference of 4.30 points lower (95% CI: 2.91 points to 5.69 points lower) on solriamfetol compared to placebo. The quality of evidence was high. (see supplemental material, Figure S25)

In the parallel design RCT, \(^\text{73}\) participants taking solriamfetol reported an estimated mean ESS difference of 6.20 points lower (95% CI: 4.01 to 8.39 points lower) than that reported in the placebo group. This was a clinically significant reduction. (see supplemental material, Table S42)

The three RCTs evaluated the effect of solriamfetol on the ability to maintain wakefulness in patients with unspecified narcolepsy using the MWT. \(^\text{72-74}\) The meta-analysis demonstrated that solriamfetol met the clinical significance threshold on the MWT with a mean difference of 10.4 minutes higher (95% CI: 8.29 to 12.50 minutes higher) when compared to placebo. The quality of evidence was high. (see supplemental material, Figure S26)

Disease Severity: All 3 studies reported on the percentage of patients with unspecified narcolepsy reporting overall improvement in Clinical Global Impression of change (CGI-C) scores. \(^\text{72-74}\) The improvement in the scores in the solriamfetol group ranged from 36.4% to 47.7% when compared to the placebo group. \(^\text{72, 73}\) This met the clinical significance threshold. The quality of evidence was high. (see supplemental material, Table 43)

Two RCTs also reported on the percentage of patients with unspecified narcolepsy reporting overall improvement in Patient Global Impression of change (PGI-c) scores. \(^\text{73, 74}\) PGI-c in the solriamfetol group was clinically significant and ranged from 41.75% to 54.7% when compared to placebo. The quality of evidence was high. (see supplemental material, Table 44)

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 overall quality of evidence for solriamfetol for the treatment of narcolepsy was considered high. Daytime sleepiness and disease severity were noted to have improved significantly in adults on solriamfetol.

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 on the use of solriamfetol in the RCTs were as follows: headache: 0.12 (95% CI: -0.18, 0.06), decreased appetite: 0.12 (95% CI: 0.07, 0.17) insomnia: 0.09 (95% CI: -0.04, 0.21) and nausea : 0.06 (95% CI: -0.04, 0.15). \(^\text{72-74}\) 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. One study reported two serious AEs in the solriamfetol treatment group (conversion disorder and acute cholecystitis) not believed to be related to study medication. \(^\text{73}\)

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

Solriamfetol is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Adequate data are not available on use of this drug in pregnant women to inform of a drug-related risk. \(^\text{75}\)

Version. 15JUNE 2020
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, co-pays, 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 one single-blind within subject cross-over study of triazolam (0.25 mg) in ten patients with NT1.76

The figures are provided in the supplemental material, Figures S27-S29. A summary of findings table is provided in the supplemental material, Table S46. 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: The RCT 76 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 0.29 minutes higher (95% CI: 3.52 minutes higher to 2.94 minutes lower) compared to placebo. This was not clinically significant. (see supplemental material, Figure S27)

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 0.22 minutes lower (95% CI: 0.35 minutes lower to 0.91 minutes higher) compared to placebo. This was also not clinically significant. (see supplemental material, Figure S28) 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 reported data for fatigue.

SLEEP QUALITY: The RCT 76 evaluated sleep quality on the basis of sleep efficiency. The mean difference in sleep efficiency in the triazolam group was 9.90% (95% CI: 3.01 to 16.79 percent higher) when compared to placebo. This was not clinically significant. Quality of evidence was moderate due to imprecision. (see supplemental material, Figure S29)

Overall Quality of Evidence
The TF felt there was possibly important uncertainty or variability on how the main outcome measure of excessive daytime sleepiness was assessed. Only objective sleepiness was assessed and there was no standardized subjective sleepiness measure reported. The quality of evidence for the treatment of narcolepsy with triazolam was moderate and downgraded due to imprecision.
**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.

No other studies included in the systematic review reported on the use of triazolam (irrespective of the indication). There is a possible risk of teratogenicity based on limited human data.

**Resource Use**
At the time of this publication, per the National Average Drug Acquisition Cost (NADAC) database, the unit cost of 0.125 mg – 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, co-pays, and deductibles.

**Patient Values and Preferences**
The TF determined there was possibly important uncertainty regarding whether or not 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.

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**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 one RCT that examined the effects of clarithromycin on 20 adult patients with central disorders of hypersomnolence, including 10 patients with idiopathic hypersomnia.\(^7^7\) The dose of clarithromycin was 1000 mg/day, divided into two doses, compared to placebo in a five week cross-over study.

The literature review also identified one retrospective observational study of clarithromycin for hypersomnia disorders.\(^7^8\) 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 two doses. Data for outcomes of these 2 studies specific to participants with idiopathic hypersomnia were obtained from personal communication via email with corresponding author, Lynn Marie Trotti, MD, MSc. in November 2018. Details of data obtained from this communication have been indicated in the supplemental material.

The figures and tables are provided in the supplemental material, Figures S30-S35 and Table S47. A summary of findings table is provided in the supplemental material, Table S48. 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.\(^7^7\) This study showed a clinically significant mean reduction of
3.3 points lower on the ESS (95% CI: 7.6 points lower to 1.0 points higher) with clarithromycin than the placebo group. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S30)

One RCT evaluated the effect of clarithromycin on excessive daytime sleepiness in patients with idiopathic hypersomnia using the Stanford Sleepiness Scale (SSS). 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 to 0.6 points higher) with clarithromycin than the placebo group. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S31)

**Disease Severity:** One observational study measured change in disease severity with clarithromycin using a scale of improved, ineffective, or stopped due to side effects. 71% 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 supplemental material, Table S47)

**Quality of Life:** One RCT evaluated the effect of clarithromycin on quality of life in patients with idiopathic hypersomnia using two different tools, the SF-36 and the Functional Outcomes of Sleep Questionnaire (FOSQ). Total SF-36 scores, calculated as an average of all sub-scores, had a clinically significant mean difference of 9.7 points higher (95% CI: 21.0 points higher to 1.6 points lower) on clarithromycin than placebo. (see supplemental material, Figure S32)

FOSQ scores showed a clinically significant difference of 1.9 points higher (95% CI: 0.5 points lower to 4.3 points higher) on clarithromycin than placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S33)

**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). 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 0.34 millisecond⁻¹ (0.37 points lower to 1.05 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 supplemental material, Figure S34)

**Fatigue:** One RCT measured the effects of clarithromycin on fatigue in patients with idiopathic hypersomnia using the SF-36 energy and vitality subscale. There was a clinically significant improvement of 14.1 points higher vitality (95% CI: 36.1 points higher to 7.9 points lower) with clarithromycin than with placebo. Quality of evidence was moderate due to imprecision. (see supplemental material, Figure S35)

**Overall Quality of Evidence**
The TF concluded that the overall quality of evidence was moderate, based on the critical outcomes reported in the RCTs and downgrading of the quality of evidence because of imprecision. Clinical significance thresholds were met for improvement in sleepiness, quality of life, and disease severity.

**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 critical outcomes- 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.77 The number of participants experiencing at least one adverse event was no different between clarithromycin and placebo treatment periods. Commonly reported adverse events included gastrointestinal symptoms; any kind (73%), dysgeusia or dysosmia (68%), nausea (32%), insomnia (27%) and diarrhea (18%). In an observational study of clarithromycin for treatment of hypersonsomolence disorders including idiopathic hypersomnia, 78 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).

Although clarithromycin does not have any black-box warnings, the US 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. 79 Clarithromycin should not be used in pregnant women except in circumstances where no alternative therapy is appropriate. Additionally, because clarithromycin is an antibiotic, risks associated with antibiotic use (e.g., 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 is $0.58/tablet and $4.04 per unit for the extended release (ER) tablet of the same dose.24 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 judgement, 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 one retrospective chart review of flumazenil for treatment of central disorders of hypersonsomolence, which included 36 patients with idiopathic hypersomnia.80 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 to 60 mg/day, divided into four doses/day. Transdermal doses ranged from 12 mg/day to 48 mg/day, divided into up to four doses/day Data for outcomes of this study specific to participants with idiopathic hypersomnia were obtained from personal communication via email with corresponding author, Lynn Marie Trotti, MD, MSc in June 2019. Details of data obtained from this communication have been indicated in the supplemental material.

The data table is provided in the supplemental material, Table S49. A summary of findings table is provided in the supplemental material, Table S50. 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.

Version. 15JUNE 2020
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. Sixty-four% of the idiopathic hypersomnia patients were judged to have symptomatic benefit from flumazenil. This was considered clinically significant. Quality was downgraded to very low due to imprecision. (see supplemental material, Table S49)

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 the study and downgrading of the quality of evidence because of imprecision.

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 hypersonmolence. 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 black box warning states that this drug has been associated with seizures. There are no adequate and well-controlled studies in pregnant women. Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Resource Use
The NADAC database has listed unit price for 0.1 mg-0.5 mg/5 ml vials as $1.26. 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 sub-lingual lozenge – for topical or mucosal absorption, respectively. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 one retrospective, observational study of methylphenidate in 61 patients with idiopathic hypersomnia. 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 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 the supplemental material, Table S51. A summary of findings table is provided in the supplemental material, Table S52. 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\(^\text{82}\) reported change in 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 supplemental material, Table 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: 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 the study and downgrading of the quality of evidence because of imprecision.

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%).\(^\text{82}\)

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%). 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%).

In addition, this drug is an FDA Schedule II federally controlled substance and has a black box warning and stating that it should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. There are no adequate and well-controlled studies in pregnant women but should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised if administered to nursing mothers.\(^\text{32}\)

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 mg-20 mg], and $1.95-3.51/capsule [10 mg-60 mg].\(^\text{24}\) Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

Patient Values and Preferences:
The TF concluded that there was probably no important uncertainty or variability in how people value the critical outcomes 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 one RCT that examined the effects of modafinil vs. placebo on 31 adult patients with idiopathic hypersomnia. This was a parallel-group study of modafinil 200 mg/day, divided into two doses. Data for outcomes of this study were obtained from personal communication via email with corresponding author, Professor Geert Mayer, in November 2018. Details of data obtained from this communication have been indicated in the supplemental material.

TF literature review also identified four observational studies of the effect of modafinil in adult patients with idiopathic hypersomnia. Three of these studies were retrospective, based on chart review and/or clinical interview. Sample sizes in these observational studies ranged from 25 to 104. One observational study was a prospective cohort with 18 patients diagnosed with idiopathic hypersomnia on modafinil. 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 by included three adolescents aged 16.6 years and older.

The meta-analyses, figures and tables are provided in the supplemental material, Figures S36-S38 and Tables S53-S55. A summary of findings table is provided in the supplemental material, Table S56. 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. This study showed a clinically significant difference of 4.0 points lower ESS in the modafinil group (95% CI: 0.7 points to 7.3 lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S36)

Two observational studies used the ESS and showed clinically significant pre-post improvements in ESS ranging from reductions of 3.0 to 6.0 points, supporting the finding of the RCT. The quality of evidence was low. (see supplemental material, Table S53)

One RCT evaluated the effect of modafinil on the ability to maintain wakefulness using the MWT. This RCT showed a clinically significant difference of 3.0 minutes longer wakefulness in the modafinil group (95% CI: 11.8 minutes longer to 5.8 minutes shorter) when compared to placebo. The quality of evidence was downgraded to low due to serious imprecision. (see supplemental material, Figure S37)

**Disease Severity:** One RCT evaluated disease severity, using the Clinical Global Impression (CGI) rating scale. This study found a clinically significant decrease in CGI severity of 1.0 point (95% CI: 0.1 to 1.9 points lower) with modafinil when compared with placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S38)

Two observational studies used study-specific scales to measure change in disease severity with modafinil treatment. One observational study (n=18) reported change in disease severity using a scale of improved, ineffective, stopped for side effects, or not followed up. Eighty-three % of the patients reported an improvement with modafinil. (see supplemental material, Table S54)

The other observational study recorded change in disease severity in 85 patients of which 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). Per the last recorded follow-up visit, only 25 patients remained on modafinil. Of the 50 patients who started treatment with modafinil, eighteen (36%) reported complete
symptomatic relief, four (8%) reported partial symptomatic relief, and three (6%) reported no benefit. (see supplemental material, Table S55) 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 was moderate based on the RCT data for critical outcomes and downgrading of the quality of evidence because of imprecision. Clinical significance thresholds were met for 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 is used for other hypersomnia disorders. One RCT reported the frequency of adverse events with modafinil in adult patients with idiopathic hypersomnia.83 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%, nausea of 4 to 13%, and combined gastrointestinal symptoms of 9 to approximately 15%.35, 82, 84

Across all RCTs included in the systematic review 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: 0.04, -0.02), 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). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.86 While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.23 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 mg – 200 mg modafinil doses ranged from $0.92 to $1.02 for each tablet.24 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 one retrospective, observational study of pitolisant for non-narcoleptic central hypersomnia. 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 and 50 mg/day, dosed once per day in the morning.

The data table is provided in the supplemental material, Table S57. A summary of findings table is provided in the supplemental material, Table S58. 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. Pitolisant resulted in a clinically significant reduction in ESS of 2.65 points (95% CI: 1.6 to 3.7 points lower). Quality of evidence was downgraded to very low due to imprecision. (see supplemental material, Table S57)

**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 a single observational study and downgrading of the quality of evidence because of imprecision.

**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 was 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%). Two patients developed depressive symptoms, one with suicidal ideation, which resolved after discontinuation of pitolisant. Therefore, the TF judged the undesirable effects to be moderate.

Across all RCTs included in the systematic review that reported on the use of pitolisant (irrespective of the indication), the commonly reported adverse events included headache (35.4%), insomnia (9.4%), and nausea (7.5%). Four AEs were considered severe: abdominal discomfort, nausea, malaise, and insomnia. Commonly reported adverse events included epigastralgia & abdominal pain (15.4%), increased appetite (14.1%), weight gain (14.1%), headaches (12.8%) and insomnia (11.5%).

Pitolisant has low abuse potential and thus is not a scheduled federally controlled substance. Studies in animals have shown reproductive toxicity, including teratogenicity. 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.
**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, co-pays, and deductibles. No included studies assessed the cost-effectiveness of pitolisant.

**Patient Values and Preferences**
The TF judged that some idiopathic hypersomnia patients 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 one retrospective, observational study assessing the effects of sodium oxybate on excessive daytime sleepiness measured by the ESS in 46 adults with idiopathic hypersomnia. The average dose of sodium oxybate at the end of titration was 4.3 gm, with 66% of patients taking a single nocturnal dose rather than twice-nightly dosing.

The data table is provided in the supplemental material, Table S59. A summary of findings table is provided in the supplemental material, Table S60. 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. Sodium oxybate resulted in a clinically significant reduction of ESS scores of 2.7 points lower (95% CI: 5.0 points lower to 0.4 points higher). Quality of evidence was very low due to imprecision. (see supplemental material, Table S59)

**DISEASE SEVERITY:** The observational study evaluated the effect of sodium oxybate on overall disease severity in patients with idiopathic hypersomnia, using a four-point scale assessing the global benefit. 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 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) 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 reporting of the critical outcome- excessive daytime sleepiness in a single observational study and downgrading of the quality of evidence because of imprecision.
**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%).

Across all RCTs included in the systematic review that reported on the use of sodium oxybate (irrespective of the indication), the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances was 0.10 (95% CI: 0.05 to 0.14), nausea was 0.10 (95% CI: 0.00 to 0.21), dizziness was 0.9 (0.04 to 0.14), urinary/renal disturbances was 0.07 (95% CI: 0.22 to 0.11), headache was 0.04 (-0.17 to 0.08) and chest discomfort was 0.02 (0.0 to 0.04). 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%). (see supplemental material, Figures S75-S82)

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. Adequate data are not available on use of this drug in pregnant women to inform drug-related risk. Animal studies have shown no evidence of teratogenicity, but embryolethality was reported. 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.

**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 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 milliliters, 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 judgement, based on sodium oxybate’s reductions in daytime sleepiness and sleep inertia, relative to its moderately severe side effect profile. The TF acknowledged some patients find twice night dosing to be inconvenient and it is unknown if sleep inertia affects patient ability to take twice night dosing.

**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 one prospective, open label, single center study that included 71 patients with Kleine-Levin syndrome (n=40 were children). 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 the supplemental material, Tables S61-S63. A summary of findings table is provided in the supplemental material, Table S64. 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, 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 10.50 episodes (95% CI: 7.68 to 13.32 episodes lower). (see supplemental material, Table S61)

The frequency of Kleine-Levin syndrome bouts decreased by 2.5 episodes per year (95% CI: 1.71 to 3.29 episodes lower) post-lithium use compared to pre-lithium use. (see supplemental material, Table S62)

The mean episode duration also decreased by 7.30 days (95% CI: 2.55 to 12.05 days lower). (see supplemental material, Table S63)

All these measures of disease severity met the threshold for clinical significance. 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 downgraded the quality of evidence for lithium therapy for Kleine-Levin syndrome to very low based on the critical outcome reported in the observational study identified in our literature review and downgrading of the quality of evidence because of imprecision.

**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 among Kleine-Levin syndrome patients, though five patients discontinued treatment because of side effects. Almost 50% of the patients treated with lithium for Kleine-Levin syndrome experienced at least one 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.

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

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. There is a possible risk of teratogenicity and neonatal harm based on human data.
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 capsule to $0.15 per unit of 600 mg capsules. The ER tablet pricing ranged from $0.15 per unit for 300 mg to $0.19 per unit of 450 mg. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 Kleine-Levin syndrome patients may favor lithium use over no treatment.

Methylprednisolone
The TF identified one observational, open-label study of Intravenous (I.V.) methylprednisolone during prolonged episodes of Kleine-Levin syndrome bouts vs. abstention. The study included 26 patients with Kleine-Levin syndrome who received 1 g/d I.V. methylprednisolone for 3 days during 1 to 6 Kleine-Levin syndrome episodes and compared effects on episode duration with 48 untreated Kleine-Levin syndrome patients. Mean ages of patients in this study ranged from 16.9-24.6 years and patients were followed for a 3-year time period.

The data tables are provided in the supplemental material, Table S6-66. A summary of findings table is provided in the supplemental material, Table 67. 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 11 days (55.14%) lower [95% CI: 56 days lower to 6 days higher) compared to the no-treatment group. This was a clinically significant reduction. (see supplemental material, Table S65)

The study showed better response if the I.V.-methylprednisolone administration was within the first 11 days of the episode. With this early treatment, the pre-post difference in the mean episode shortening was 12 episodes lower (95% CI: 68 episodes lower to 3 episodes higher) when compared to the non-treatment group. (see supplemental material, Table 66)

Quality of evidence for both these measures was rated down to 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 overall quality of evidence for I.V. methylprednisolone to treat Kleine-Levin syndrome compared to placebo was very low, based on the critical outcomes reported in the open-label study and downgrading of the quality of evidence because of imprecision.

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 one 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, nervousness/restlessness, but no manic switching. None of these symptoms required any specific management.

No other studies included in the systematic review reported on the use of I.V. methylprednisolone (irrespective of the indication). There is a possible risk of low birth weight or prematurity based on limited human data.

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

**Patient's 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.

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**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. 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**
Presented below are summaries of evidence identified in literature searches and the statistical analyses for hypersomnia secondary to Parkinson disease and Dementia with Lewy bodies (DLB).

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

The data figures and tables are provided in the supplemental material, Tables S68-S69. A summary of findings table is provided in the supplemental material, Table S70. 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 one 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 2.99 to 9.01 points lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S68)
The same study demonstrated a clinically significant mean pre- to post-treatment difference on the MWT of 10.40 minutes higher (95% CI: 4.43 minutes to 16.37 minutes higher). The quality of evidence was very low due to imprecision. (see supplemental material, Table S69)

**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 overall quality of evidence for armodafinil for the treatment of hypersomnia secondary to DLB was very low, based on the critical outcome reported in the observational study and downgrading of the quality of evidence because of imprecision.91

**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.91

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 0.11 (95% CI: 0.01 to 0.22) indicating greater risk of headache for armodafinil. (see supplemental material, Figure S65) Other commonly reported adverse events in the RCTs included: nausea (10.7%), upper respiratory tract infection (9%), 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%). The more serious but rare AEs reported in product information for armodafinil, such as Stevens Johnsons 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. Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes.92 Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. While armodafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.23 Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy. The AASM has 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 to $1.18.24 Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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,91 the TF felt that patients would most likely favor armodafinil use.
Light Therapy
The TF identified one RCT of bright light therapy (vs. dim light) for treatment of subjective excessive daytime sleepiness and fatigue that included 16 participants with Parkinson disease.\textsuperscript{93}

The data figures are provided in the supplemental material, Figure S39-S40. A summary of findings table is provided in the supplemental material, Table S71. 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 one RCT for the assessment of excessive daytime sleepiness in patients with hypersomnia secondary to Parkinson disease using the ESS.\textsuperscript{93} The mean difference on the ESS was 1.77 points lower (95\% CI: 4.68 points lower to 1.14 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 supplemental material, Figure S39)

**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 one RCT for the assessment of fatigue in patients with hypersomnia secondary to Parkinson disease using the Fatigue severity scale (FSS). The mean difference on the FSS in the light therapy group was 1.39 points higher (95\% CI: 7.49 points lower to 10.27 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 supplemental material, Figure S40)

**Overall Quality of Evidence**
The TF rated the overall quality of evidence for the use of bright light therapy to treat hypersomnia secondary to Parkinson disease as moderate, based on the critical outcomes reported in the RCT and downgrading of the quality of evidence because of imprecision.\textsuperscript{93}

**Benefits and Harms**
The TF determined that the balance between the desirable and undesirable effects was inconclusive in patients with hypersomnia secondary to Parkinson disease. Two of the 16 patients randomized to bright light therapy reported 1 adverse effect each: headache and sleepiness; both of these resolved spontaneously.\textsuperscript{93}

**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, co-pays, 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 due to Parkinson disease would use light therapy to treat their disease.

**Modafinil**
The TF identified 4 RCTs which examined the effect of modafinil vs. placebo on a total number of 122 adult patients with hypersomnia secondary to Parkinson disease.\textsuperscript{94-97} 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 one observational study on the effect of modafinil in adult patients with hypersomnia secondary to Parkinson disease. The sample size in this study was 10. Modafinil doses varied between 100-400 mg/day.

The meta-analyses and figures and tables are provided in the supplemental material, Figures S41-S45 and Table S72. A summary of findings table is provided in the supplemental material, Table S73. 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 disease using the ESS. The meta-analysis showed a clinically significant mean difference of 2.25 points lower (95% CI: 0.69 to 3.80 points lower) ESS in patients on modafinil compared to control. The quality of evidence was moderate and downgraded due to imprecision. (see supplemental material, Figure S41)

A single observational study on the effect of modafinil in patients with Parkinson disease noted a clinically significant decrease of 8.22 points (95% CI: 11.97 points lower to 4.47 points higher) on the ESS. The quality of evidence was very low due to imprecision. (see supplemental material, Table S72)

One RCT compared the effect of modafinil to placebo in patients with Parkinson disease using the MWT. There was an increase of 1.77 minutes (95% CI: 10.24 minutes higher to 6.70 minutes lower) when compared to placebo, which was not clinically significant. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S42)

One RCT compared the effect of modafinil to placebo in patients with Parkinson disease using the MSLT. There was an insignificant clinical change of 0.80 minutes higher (95% CI: 3.06 minutes higher to 1.46 minutes lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S43)

**Quality of Life:** The TF identified one RCT with patients with Parkinson disease utilizing a total score of the SF-36 to assess quality of life. It demonstrated a reduction of 0.20 points lower (95% CI: 8.32 points higher to 7.92 points lower) which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision. (see supplemental material, Figure S44)

**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 disease compared the effect of modafinil to placebo on fatigue as measured by the FSS. The meta-analyses demonstrated a mean difference of 0.22 points lower (95% CI: 1.26 points lower and 0.83 points higher), which was not clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S45)

**Overall Quality of Evidence**
The TF concluded that the overall quality of data on modafinil for patients with Parkinson disease was moderate based on the critical outcomes reported in the RCTs and downgrading of the quality of evidence because of imprecision.
**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 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, 0.15). One RCT \(^9^6\) reported three serious AEs of hematuria, three AEs of memory loss, and three AEs of feeling off balance out of nine patients with Parkinson disease. One observational study reported headaches, visual hallucinations, sleep attacks and generalized tingling (all approximately in 10% cases). \(^9^8\) 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 included in the systematic review 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: 0.04, -0.02), 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). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.\(^8^6\) While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero.\(^2^3\) 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 mg - 200mg doses ranged from is $0.92-1.02 for each tablet. \(^2^4\) Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 disease given higher rates of more serious AEs reported.

**Sodium oxybate**

The TF identified one randomized, double blind, placebo-controlled, cross-over phase 2a study assessing the effects of sodium oxybate in 12 patients with Parkinson disease. \(^9^9\) Doses of sodium oxybate were titrated between 3-9 grams per night with a 2-4-week washout period. Outcomes assessed in this study included ESS, MSLT and FSS scores.

The figures and tables are provided in the supplemental material, Figures S46-S48. A summary of findings table is provided in the supplemental material, Table S74. 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 RCT\(^99\) reported that patients with Parkinson disease taking sodium oxybate had a clinically significant mean reduction of 4.20 points lower (95% CI: 6.41 to 1.99 lower) on the ESS compared to control. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure 46)

In the same study, patients also had a clinically significant mean difference on the MSLT of 2.90 minutes higher (95% CI: 1.30 to 4.50 minutes higher) compared to the placebo group. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S47)

**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 RCT\(^99\) reported a mean difference on the FSS of 0.10 points lower (95% CI: 0.66 lower to 0.86 higher) compared to placebo, which was not clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S48)

**Overall Quality of Evidence**

The TF rated the overall quality of evidence as moderate based on the critical outcomes and downgrading of the quality of evidence because of imprecision.

**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 disease.

All patients with hypersomnia secondary to Parkinson disease experienced side effects while receiving sodium oxybate. \(^99\) The majority of participants rated these side effects as 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 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 product information for sodium oxybate, such as respiratory depression, suicidality and death, were not reported in the individual studies.

Across all RCTs included in the systematic review that reported on the use of sodium oxybate (irrespective of the indication), the risk difference between sodium oxybate and placebo for occurrence of a variety of sleep disturbances was 0.10 (95% CI: 0.05 to 0.14), nausea was 0.10 (95% CI: 0.00 to 0.21), dizziness was 0.9 (0.04 to 0.14), urinary/renal disturbances was 0.07 (95% CI: 0.22 to 0.11), headache was 0.04 (-0.17 to 0.08) and chest discomfort was 0.02 (0.0 to 0.04). (see supplemental material, Figures S75-S82) 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%).

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 Adequate data are not available on use of this drug in pregnant women to inform of a drug-related risk. Animal studies have shown no evidence of teratogenicity, but embryolethality was reported. 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. \(^70\)
**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 a program called 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, co-pays, and deductibles.

**Patient’s 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**
Presented below are summaries of evidence obtained in literature searches and the statistical analyses for hypersomnia associated with traumatic brain injury (TBI).

**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. 100 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 adverse events).

The data figures and tables are provided in the supplemental material, Figures S49-S50. A summary of findings table is provided in the supplemental material, Table S75. 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, 100 armodafinil use by patients with TBI yielded a mean difference of 0.68 points lower (95% CI: 3.19 lower to 1.83 points higher) on the ESS compared to placebo. This difference was not clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S49)

The overall mean sleep latency from baseline to final visit in the above RCT using the MSLT yielded a clinically significant mean difference of 2.29 minutes higher (95% CI: 0.43 to 4.15 minutes higher) when compared to placebo. The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S50)

**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 rated the overall quality of evidence for armodafinil for the treatment of hypersomnia due to TBI as moderate, based on the critical outcome reported in the RCT. 100 The quality of evidence was downgraded because of imprecision.

Version. 15JUNE 2020
**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 to 0.24) compared to placebo. This risk difference was comparable to the overall armodafinil meta-analysis of headache side effect across different CNS hypersomnia patient groups. 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, one TBI patient developed a moderate psychotic disorder and this resolved after drug discontinuation.

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 0.11 (95% CI: 0.01 to 0.22) indicating greater risk of headache for armodafinil. Other commonly reported adverse events in the RCTs included: nausea (10.7%), upper respiratory tract infection (9%), 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%). The more serious but rare AEs reported in product information for armodafinil, such as Stevens Johnsons 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. Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. While armodafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 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**

Per the NADAC database, the unit cost of 50 and 250 mg doses ranged from $0.26 to $1.18. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 measure of excessive daytime sleepiness, the TF determined that patients would most likely favor armodafinil use.

**Modafinil**

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

The meta-analyses and figures and tables are provided in the supplemental material, Figures S51-S53. A summary of findings table is provided in the supplemental material, Table S76. 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. The study reported a clinically significant decrease of 3.00 points (95% CI: 1.19 to 4.81 points lower) on the ESS. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S51)

One RCT compared the effect of modafinil to placebo in patients with TBI by using the MWT to assess objective sleepiness. There was a clinically significant increase of 8.00 minutes (95% CI: 15.08 minutes higher to 0.92 minutes lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, 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. 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. The study demonstrated a clinically significant mean difference of 0.80 points lower (95% CI: 0.08 to 1.52 points lower). The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S53)

Overall Quality of Evidence
The TF concluded that the overall quality of evidence of data on modafinil for patients with TBI was moderate based on the critical outcomes reported in the RCTs. The level of evidence was downgraded for imprecision.

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 included in the systematic review 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: 0.04, -0.02), 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), and dry mouth- 0.02 (95% CI: -0.02 to 0.07). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus. While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 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 mg – 200 mg doses ranged from is $0.92-1.02 for each tablet. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

Version. 15JUNE 2020
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
Presented below are summaries of evidence obtained in literature searches and the statistical analyses for hypersomnia associated with myotonic dystrophy.

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. A total of 17 participants completed this randomized, double-blind, placebo-controlled, 3-week crossover trial.

The data figures are provided in the supplemental material, Figure S54. A summary of findings table is provided in the supplemental material, Table S77. 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 one RCT reporting on excessive daytime sleepiness using the ESS in adult participants with myotonic dystrophy. It demonstrated a mean difference of 1.36 points lower (4.28 points lower to 1.56 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 supplemental material, Figure 54)

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 found the overall quality of evidence for methylphenidate for the treatment of hypersomnia in adult participants with myotonic dystrophy to be moderate based on the critical outcome reported in the RCT and downgrading of the quality of evidence because of imprecision.

Benefits and Harms
The TF concluded 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. 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 (1, diarrhea; 2, nervousness and irritability). Overall, the more serious but rare adverse events reported in product information for methylphenidate such as depression and psychosis were not reported in the included study.

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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%). 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%).

In addition, this drug is an FDA Schedule II federally controlled substance and has a black box warning and stating that it should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. There are no adequate and well-controlled studies in pregnant women but should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised if administered to nursing mothers.32

**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 mg-20 mg], and $1.95-3.51/capsule [10 mg-60 mg]. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patient's Values and Preferences**

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

**Modafinil**

The TF identified two RCTs which examined the effect of modafinil on patients with myotonic dystrophy. Sample sizes ranged from 19-28 and modafinil doses ranging from 200-300 mg.103,104 The meta-analyses and figures and tables are provided in the supplemental material, Figures S55-S61. A summary of findings table is provided in the supplemental material, Table S78. 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 two studies comparing the effect of modafinil in patients with myotonic dystrophy103,104 demonstrated a clinically significant decrease of 3.60 points [95% CI: 1.52 to 5.67 points lower] on the ESS. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S55)

A meta-analysis of two studies compared the effect of modafinil to placebo in patients with myotonic dystrophy by using the MWT.103,104 There was a clinically significant increase of 5.79 minutes (95% CI: 16.23 minutes higher to 4.64 minutes lower) when compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S56)

One RCT compared the effect of modafinil to placebo in patients with myotonic dystrophy using the MSLT103 reporting a change of 0.26 minutes lower (95% CI: 3.77 minutes higher to 4.29 minutes lower) when compared to placebo, which was not clinically significant. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S57)

**QUALITY OF LIFE:** One RCT with patients with myotonic dystrophy103 utilizing a total score of the SF-36 reported a reduction of 1.81 points (95% CI: 3.31 points higher to 5.41 lower) which was not clinically significant. The quality of evidence was downgraded to low due to serious imprecision. (see supplemental material, Figure S58)
Another RCT with patients with myotonic dystrophy demonstrated a reduction in the mean difference for the mental component of the SF-36 of 0.32 points (95% CI: 7.83 points higher to 8.47 points lower) and a mean difference for the SF-36 physical component of 2.44 points higher (95% CI: 12.92 points higher to 8.04 points lower). Neither the mental nor physical component scores met clinical significance. The quality of evidence was downgraded to low due to serious imprecision. (see supplemental material, Figures S59, S60)

**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. The study reported a clinically significant mean increase of 10.69 points (95% CI: 22.45 points higher to 1.07 points lower). The quality of evidence was moderate due to imprecision. (see supplemental material, Figure S61)

**Overall Quality of Evidence**
The overall quality of evidence of data on modafinil for patients with myotonic dystrophy was moderate based on the critical outcomes reported in the RCTs. The level of evidence was downgraded for imprecision.

**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, one RCT reported the following adverse events: diarrhea, insomnia, spatial disorientation, acne and weight loss (in about 8% of the cases). 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.

Across all RCTs included in the systematic review 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: 0.04, -0.02), 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). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus. While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 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 mg - 200mg doses ranged from is $0.92-1.02 for each tablet. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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 Parkinson’s disease patients given higher rates of more serious AEs reported.

**Selegiline**
The TF identified one RCT with a total of 20 adult participants with myotonic dystrophy. Dose of selegiline was 20 mg.

The figure is provided in the supplemental material, Figure S62. A summary of findings table is provided in the supplemental material, Table S79. 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. The study did not demonstrate a clinically significant improvement in favor of selegiline. The mean difference between selegiline and placebo was 3.70 minutes lower on the MSLT (95% CI: 8.83 lower to 1.43 higher) indicating selegiline made patients sleepier than controls. The quality of evidence was rated moderate due to imprecision. (see supplemental material, Figure S62)

**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 to be low based on the critical outcome in the RCT and downgrading of the quality of evidence because of serious imprecision.

**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% male patients had difficulty with micturition. The more serious but rare AEs reported in 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%). The adverse events required neither treatments nor the interruption of the study drug. Commonly reported adverse events reported in two observational studies identified on the use of selegiline included headache (13%) and irritability (5%). Adequate data are not available on use of this drug in pregnant women to inform of a drug-related risk.

Finally, selegiline is a monoamine oxidase-B inhibitor and should not be taken with medications that could result in serotonin syndrome (e.g., SSRIs). Adequate data are not available on use of this drug in pregnant women to inform of a drug-related 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, co-pays, and deductibles.

Version. 15JUNE 2020
Patient’s 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 potential to change to severe effects.

Hypersomnia secondary to brain tumors, infections, or other central nervous system lesions
Presented below are summaries of evidence obtained in literature searches and the statistical analyses for hypersomnia associated with multiple sclerosis.

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

The data tables are provided in the supplemental material, Tables S80-S81. A summary of findings table is provided in the supplemental material, Table S82. 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 4.80 points (95% CI: 3.41 points to 6.19 points lower) on the ESS. The quality of evidence was very low due to imprecision. (see supplemental material, Table S80)

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: 2.25 to 7.55 points lower) on the FSS. The quality of evidence was very low due to imprecision. (see supplemental material, Table S81)

Overall Quality of Evidence
The overall quality of evidence of data on modafinil for patients with multiple sclerosis was very low. The level of evidence was downgraded for imprecision for critical outcome of excessive daytime sleepiness.

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

Across all RCTs included in the systematic review 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: 0.04, -0.02), 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). (see supplemental material, Figures S66-S73)

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus. While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil version. 15JUNE 2020
Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. Based on these findings, Health Canada updated the Canadian Product Monograph (CPM) to include a contraindication to the use of modafinil in pregnancy. The AASM has reached out to Teva Pharmaceutical Industries Ltd. (makers of modafinil) to gather more information and contacted the FDA requesting additional guidance be provided for health care professionals in the U.S.

**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. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patient Values and Preferences**
The TF felt that there were probably important uncertainty or variability in patient values and preferences for this treatment. Because data were insufficient for decision making, the TF was uncertain whether patients with hypersomnia secondary to multiple sclerosis would opt for or against treatment with modafinil over no treatment.

**Hypersomnia secondary to endocrine disorder**
Presented below are summaries of evidence obtained in literature searches and the statistical analyses for hypersomnia secondary to Type 2 Diabetes Mellitus (Type 2 DM).

**Liraglutide**
The TF identified one open-label retrospective study of injectable liraglutide for the treatment of excessive daytime sleepiness in 158 adult patients with Type 2 DM. This study reported the pre- and post-treatment effect of liraglutide in 158 patients over a 3-month time period.

The data tables are provided in the supplemental material, Table S83. A summary of findings table is provided in the supplemental material, Table S84. 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 one observational study for the assessment of excessive daytime sleepiness using the ESS. After 3 months of treatment, patients with Type 2 DM had a mean ESS reduction of 1.50 points (95% CI: 0.61 to 2.39 points lower) with use of liraglutide compared to pre-treatment. This difference did not meet the clinical significance threshold. The quality of evidence was very low due to imprecision. (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 rated overall quality of evidence for liraglutide for the treatment of hypersomnia in patients with Type 2 DM as very low, based on the critical outcome reported in the observational study and downgrading of the quality of evidence because of imprecision.
**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.

No other studies included in the systematic review reported on the use of liraglutide (irrespective of the indication). Adequate data are not available on use of this drug in pregnant women to inform of a drug-related risk.

**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. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, 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.

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**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 which 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 controls (n=13). 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 controls received light therapy for 15 minutes daily, for a period of 14 days. Measured illumination was approximately 3300 lux at eye level. Subjects received standardized instructions for behaviors during the treatment protocol.

The table is provided in the supplemental material, Table S85. A summary of findings table is provided in the supplemental material, Table S86. 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 post-treatment. The TF compared the pooled baseline data with the pooled post intervention data. The pre- post difference was 0.89 points lower (95% CI: 0.27 to 1.51 points lower). This was not clinically significant. The evidence was downgraded to moderate due to imprecision. (see supplemental material, Table S85)
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 the RCT. Gleaned data may not be generalizable to male populations, as only females were included in the sole identified study. The study was downgraded to moderate due to imprecision.

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, co-pays, and deductibles.

Patient's 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 which 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). In the double-blind, placebo-controlled parallel group investigation (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), the authors utilized the same parameters as primary outcomes (ESS and FSS). These 2 RCTs had modest sample sizes ranging from n=72 to 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. The first study (n=31) was 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 (n=29) was comprised of patients with active depression. These two 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 the supplemental material, Figures S63-S64 and Tables S87-S90. A summary of findings table is provided in the supplemental material, Table S91. 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 on 72 patients with excessive daytime sleepiness and MDD. The data demonstrated a clinically insignificant mean ESS difference of 0.80
points lower (95% CI: 2.69 points lower to 1.09 points higher) in the modafinil group when compared to placebo over a treatment period of 6 weeks. (see supplemental material, Figure S63) In the other RCT, 109 136 patients with partially treated MDD received 100 mg modafinil on days 1-3, 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 post-intervention data were displayed in a figure. The estimated calculations demonstrated a clinically insignificant mean ESS difference of 1.70 points lower (95% CI: 0.58 to 2.82 points lower) at Week 6. The quality of evidence based on these 2 studies was considered moderate due to imprecision. (see supplemental material, Table S87)

One open-label study conducted weekly ESS evaluations for a period of 6 weeks among 29 patients with MDD. 112 Modafinil was initiated at a dose of 100 mg/d for days 1-3, and titrated from day 4 to a maximum dose of 200 mg/d. If “clinically indicated,” the modafinil dosage was reduced to 100mg/d or changed to 100 mg twice daily. Only baseline raw data were provided. The post 6-week treatment data was displayed in a figure. Estimated calculations demonstrated a clinically significant mean pre-post difference of 5.50 points lower (95% CI: 2.60 to 8.40 points lower) in ESS at the study endpoint. The quality of evidence was considered very low due to imprecision. (see supplemental material, Table S88)

QUALITY OF LIFE: An open-label study of patients with MDD and fatigue +/- sleepiness conducted weekly evaluations for a period of 6 weeks. 112 Only post treatment 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, 110 measured the effects of modafinil on fatigue in patients with MDD with the FSS. There was a clinically insignificant improvement of 0.1 points reduction (95% CI: 0.85 points lower to 0.65 points higher) with modafinil than with the placebo group. The quality of evidence was deemed moderate and was downgraded due to imprecision. (see supplemental material, Figure S64)
The other RCT109 was 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 0.35 decrease. This was not clinically significant. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Table S89)

Fatigue was also evaluated using the FSS in an open-label study of patients with MDD.112 Estimated calculations demonstrated a clinically significant mean FSS difference of 2.20 points lower (95% CI: 1.24 to 3.16 points lower) at the study endpoint. The quality of evidence was very low due to imprecision. (see supplemental material, Table S90)

**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 was moderate based on the critical clinical outcomes reported in the RCTs and downgrading of the quality of evidence because of imprecision.

**Benefits and Harms**
The TF determined that the balance between the desirable and undesirable effects is 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 two RCTs109, 110 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 cases of suicidal ideation were reported in the Dunlop et al publication (one reported a serious adverse event because hospitalization was required).

Across all RCTs included in the systematic review 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: 0.04, -0.02), 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). (see supplemental material, Figures S66-S73) Based on animal studies, fetal developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus.

While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 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 mg – 200 mg doses ranged from $0.92-1.02 for each tablet. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patient's Values and Preferences**

No specific data exists 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. 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 two observational studies that examined the effect of modafinil in pediatric patients with narcolepsy type 1. The average age at diagnosis in one study was 11.8 ± 0.5 years and that in the other study was 11.8 ± 3.3 years.

The tables are provided in the supplemental material, Tables S92-S94. A summary of findings table is provided in the supplemental material, Table S95. 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 and accident risk, 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. The mean pre-post ESS score in patients with NT1 on modafinil demonstrated a
clinically significant improvement of 4.09 points lower (95% CI: 8.01 to 0.18 points lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S92)

The aforementioned observational study also assessed sleepiness using the MSLT. The mean MSLT score in the pediatric patients was 0.44 minutes higher (95% CI: 1.2 minutes higher to 0.33 minutes lower), This was not clinically significant. The quality of evidence was very low due to imprecision. (see supplemental material, Table S93)

**Disease Severity:** One observational study used a 7-point scale to record sleepiness severity. On a scale of -3 to 3, -3 was maximal negative effect, 0 was no effect, and 3 was maximal positive effect. The study demonstrated a clinically significant improvement of 1.9 points higher (95% CI: 1.7 to 2.1 points higher) with modafinil. The quality of evidence was very low due to imprecision. (see supplemental material, Table S94)

**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 concluded that the quality of evidence for modafinil for the treatment of narcolepsy in pediatric patients was very low based on the critical outcomes reported in the observational studies and downgrading of the quality of evidence because of imprecision.

**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: 0-10%. No severe reactions were reported. Cases of psychosis and Steven Johnson syndrome (severe) limit FDA approval of modafinil for patients <17 years of age.

Finally, this medication is an FDA Schedule IV federally controlled substance because of its potential for abuse or dependency. Based on animal studies, developmental toxicity was observed at clinically relevant exposures. This drug should be used during pregnancy only if the potential benefit justifies the possible risk to the fetus. While modafinil is classified as Category C by FDA, a 2018 annual report of the ongoing armodafinil/modafinil Pregnancy Registry in the United States showed higher rate of major congenital anomalies, and other adverse reactions, in children exposed to the drug in utero. 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 mg – 200 mg doses ranged from is $0.92-1.02 for each tablet. Medication cost to any given patient is uncertain and determined by insurance coverage, co-pays, and deductibles.

**Patient's 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 7–17yrs) that examined changes in daytime sleepiness, disease severity and weekly cataplexy episodes in pediatric patients with NT1.115

The literature search also identified four observational studies examining the effect of sodium oxybate in pediatric patients with NT1.113, 116-118 Sample sizes varied between 10 and 31 and sodium oxybate doses in the 5 ± 2 g range.

The meta-analyses and figures and tables are provided in the supplemental material, Figures S83-S84 and Tables S96-S100. A summary of findings table is provided in the supplemental material, Table S101. 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 the NT1 pediatric population using the ESS for Children and Adolescents (ESS-CHAD) in 63 of the 104 participants.115 The mean ESS-CHAD score in pediatric patients with NT1 on sodium oxybate was clinically significant at 2.65 points lower (95% CI: 1.3 to 4.0 points lower) compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S83)

Two observational studies116, 118 also showed a clinically significant pre-post difference of 5.42 points to 6.9 points lower in the mean ESS-CHAD. The quality of evidence was very low due to imprecision. (see supplemental material, Table S96)

One observational study conducted the assessment of sleepiness in by using the MSLT.117 The mean MSLT score in the pediatric patients on sodium oxybate (n=13) was clinically significant difference at 1.80 minutes higher (95% CI: 4.42 minutes higher to 0.82 minutes lower). The quality of evidence was very low due to imprecision. (see supplemental material, Table S97)

Cataplexy: One RCT evaluated the change in weekly cataplexy episodes after the withdrawal of sodium oxybate in pediatric patients with NT1 using sleep diaries.115 The study demonstrated a clinically significant 327.3% increase in weekly cataplexy rate following the abrupt cessation of sodium oxybate therapy in these patients when compared with those who continued on SXB. This increase was clinically significant. The quality of evidence was moderate due to imprecision. (see supplemental material, Table S98)

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.119 The % difference in mean cataplexy reduction was noted to be 97.2% when compared with placebo. The quality of evidence for these 2 observational studies was very low due to imprecision. (see supplemental material, Table S99)

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.117 The % difference in mean cataplexy reduction was noted to be 94.87% when compared with placebo. The quality of evidence for these 2 observational studies very was low due to imprecision. (see supplemental material, Table S100)

Disease Severity: One RCT reported on disease severity based on the CGI-C (cataplexy severity) score. The mean score in pediatric patients with narcolepsy was clinically significant at 1.10 points higher [95% CI: 0.53 to 1.67 points higher] compared to placebo. The quality of evidence was downgraded to moderate due to imprecision. (see supplemental material, Figure S84)
**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 RCTs and downgrading of the quality of evidence because of imprecision. 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, one study observed weight loss in about 10% of the subjects. This is of moderate concern as the TF noted that obesity is a common co-morbidity of narcolepsy and some weight loss may be a desirable effect. Central sleep apnea with AHI > 10 was seen in 6% of the patients. Other commonly reported adverse events were enuresis (21% of sodium oxybate-naive 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 subjects and included tremor, blurred vision, increased night awakenings and nightmares. Thirteen percent discontinued sodium oxybate therapy due to nausea, constipation, and dissociative feelings.

The US 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. Adequate data are not available on use of this drug in pregnant women to inform drug-related risk. Animal studies have shown no evidence of teratogenicity, but embryolethality was reported. 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.

**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 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 milliliters, 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, co-pays, and deductibles.

**Patient’s 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 one non-randomized, open label, controlled, longitudinal observational study of IVIG use in pediatric narcolepsy (n=22) compared to controls (n=30). The table is provided in the supplemental material, Table S10. A summary of findings table is provided in the supplemental material, Table S10. 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 two years following IVIG treatment.

**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 2.65 points higher [0.56 to 4.74 points higher]. This met the clinical significance threshold. The quality of evidence was downgraded to very low due to imprecision. (Table S102)

**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 was very low based on data available on critical outcomes. The quality of evidence was downgraded because of imprecision.

**Benefits and Harms**

The use of IVIG demonstrated improvements in disease severity on the CGI-s scale but demonstrated no other beneficial effects on narcolepsy symptoms. There was no mention of medication side-effects.

**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’s Values and Preferences**

The TF felt that there was probably no important uncertainty or variability in how people value the main outcomes. But there was 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 is 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 hypersomnia, 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. Because most CNS hypersomnia 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 \( e.g., \) downgrading high to moderate \( \) but did not downgrade twice \( e.g., \) 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 hypersomnia treatment efficacy is a complex task requiring clinical expertise and patient input. Unfortunately, limited data exist addressing patient values and the outcome measures that patients and caregivers prioritize most highly. The TF pre-specified 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 or widely used in clinical practice could not be addressed in this review, such as SSRI/SNRIs for cataplexy associated with narcolepsy type 1 or traditional stimulants for idiopathic hypersomnia. The absence of inclusion of such interventions in this review should not be misinterpreted as a statement against their clinical use.

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 exists about whether to place greater weight on subjective or objective assessments, because they do not correlate consistently 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. Included subjective measures typically focused on reductions in sleepiness, a clearly meaningful outcome. However, patients also value improvements in other aspects of disease severity that were less frequently included in studies. Some 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, 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 (CST) on published literature. When such data was lacking, the TF created MCIDs based on our collective clinical experience. Such thresholds were typically conservative because the TF desired to identify even modest treatment effects. Also, 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 MCIDs on current outcome measures ensuring guideline documents focus on aspects of disease mattering most to patients.

Additional challenges arose when assessing treatment efficacy by hypersomnia diagnosis. The TF recognizes that NT1 and NT2 are two distinct conditions with different pathophysiology and significant variability in symptomology. However, most narcolepsy studies included patients with both disorders, and many failed to provide separate data for the two 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. In contrast to studies only assessing narcolepsy, for studies including any other CNS hypersomnia conditions where data were reported in aggregate \( e.g., \) clarithromycin for NT2 or idiopathic hypersomnia), only disease-specific data

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were used for this review. If disease-specific data could not be obtained (e.g., modafinil for NT1, NT2 or idiopathic hypersomnia), the study was excluded.

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 incompletely 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 non-therapeutic medication doses (e.g., sodium oxybate for narcolepsy). There were also insufficient data in most studies to perform meta-analysis of adverse side 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 is low enough at 2.4 cases per 1000 person years). Thus, practitioners are advised to carefully evaluate current general adverse effects of treatments in the context of individual patient needs. Information on post-marketing adverse effects are not available for newer treatments such as pitolisant and solriamfetol, further limiting risk/benefit assessments. Lastly, 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.

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 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. The low cost of these therapies is attractive, and these treatments are already commonly used across the world. As promoting evidence-based recommendations become 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 MCIDs 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 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 18 years of age. 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 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 behavior 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 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 non-pharmacological management of symptoms is needed to further bolster disease management and coping with chronic symptoms. Collaborations between patient groups, health care providers, researchers, government funding agencies, and industry will be necessary to spur treatment progress.
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