

# Treatment of Narcolepsy and other Hypersomnias of Central Origin

An American Academy of Sleep Medicine Review

Merrill S. Wise, MD<sup>1</sup>; Donna L. Arand, PhD<sup>2</sup>; R. Robert Auger, MD<sup>3</sup>; Stephen N. Brooks, MD<sup>4</sup>; Nathaniel F. Watson, MD<sup>5</sup>

<sup>1</sup>Methodist Healthcare Sleep Disorders Center, Memphis, Tennessee; <sup>2</sup>Wright State University, Dayton, OH; <sup>3</sup>Mayo Clinic College of Medicine, Rochester, MN; <sup>4</sup>Stanford Sleep Disorders Clinic, Stanford, CA; <sup>5</sup>University of Washington, Seattle, WA

**Objective:** The purpose of this paper is to summarize current knowledge about treatment of narcolepsy and other hypersomnias of central origin.

**Methods:** The task force performed a systematic and comprehensive review of the relevant literature and graded the evidence using the Oxford grading system. This paper discusses the strengths and limitations of the available evidence regarding treatment of these conditions, and summarizes key information about safety of these medications. Our findings provide the foundation for development of evidence-based practice parameters on this topic by the Standards of Practice Committee of the American Academy of Sleep Medicine.

**Results:** The majority of recent papers in this field provide information about use of modafinil or sodium oxybate for treatment of sleepiness associated with narcolepsy. Several large randomized, placebo-controlled studies indicate that modafinil and sodium oxybate are effective for treatment of hypersomnia due to narcolepsy. We identified no studies that report direct comparison of these newer medications versus traditional stimulants, or that indicate what proportion of patients treated initially with these medications require transition to traditional stimulants or to combination therapy to achieve adequate alertness. As with the traditional stimulants, modafinil and sodium oxybate provide, at best, only moderate improvement in alertness rather than full restoration of alertness in patients with narcolepsy. Several large randomized placebo-controlled stud-

ies demonstrate that sodium oxybate is effective for treatment of cataplexy associated with narcolepsy, and earlier studies provide limited data to support the effectiveness of fluoxetine and tricyclic antidepressants for treatment of cataplexy. Our findings indicate that very few reports provide information regarding treatment of special populations such as children, older adults, and pregnant or breastfeeding women. The available literature provides a modest amount of information about improvement in quality of life in association with treatment, patient preferences among the different medications, or patient compliance.

**Conclusion:** Several recent studies provide evidence that modafinil and sodium oxybate are effective for treatment of hypersomnia due to narcolepsy. No studies were identified that report direct comparison of these newer medications with traditional stimulants. Despite significant advances in understanding the pathophysiology of narcolepsy, we do not have an ideal treatment to restore full and sustained alertness. Future investigations should be directed toward development of more effective and better tolerated therapies, and primary prevention.

**Keywords:** Hypersomnia, narcolepsy, cataplexy, modafinil, sodium oxybate, stimulants

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## TABLE OF CONTENTS

### 1.0 Introduction

#### 1.1 Purpose

#### 1.2 Causes of excessive sleepiness

### 2.0 Background

### 3.0 Methods

#### 3.1 Literature search strategy

#### 3.2 Evidence review

### 4.0 Results

#### 4.1 Treatment of hypersomnia due to narcolepsy with or without cataplexy

##### 4.1.1 Medications

##### 4.1.1.1 Amphetamine, methamphetamine, dextroamphetamine methylphenidate, and related preparations

##### 4.1.1.2 Modafinil and armodafinil

##### 4.1.1.3 Sodium oxybate

##### 4.1.1.4 Selegiline

##### 4.1.1.5 Reboxetine

##### 4.1.1.6 Ritanserin

##### 4.1.1.7 Pemoline

#### 4.1.2 Scheduled naps plus stimulants versus stimulants alone

### 4.2 Treatment of cataplexy

#### 4.2.1 Sodium oxybate

#### 4.2.2 Medications other than sodium oxybate

### 4.3 Treatment of disrupted nocturnal sleep associated with narcolepsy

#### 4.3.1 Sodium oxybate

#### 4.3.2 Hypnotic medications

### 4.4 Treatment of hypnagogic hallucinations and sleep paralysis associated with narcolepsy

#### 4.4.1 Sodium oxybate

#### 4.4.2 Antidepressant medications

### 4.5 Studies with quality of life data

### 4.6 Treatment of hypersomnia associated with narcolepsy due to medical conditions

### 4.7 Treatment of hypersomnia due to recurrent hypersomnia

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Address correspondence to: Standards of Practice Committee, American Academy of Sleep Medicine, One Westbrook Corporate Center, Suite 920, Westchester IL 60154, Tel: (708) 492-0930, Fax: (780) 492-0943, E-mail: aasm@aasmnet.org

- 4.8 *Treatment of hypersomnia due to idiopathic hypersomnia*
- 4.9 *Treatment of hypersomnia due to medical conditions*
- 4.10 *Comprehensive management approach for narcolepsy and other hypersomnias*

**5.0 Adverse Side Effects and Safety Considerations**

**5.1 Alerting agents**

- 5.1.1 *Modafinil*
- 5.1.2 *Armodafinil*
- 5.1.3 *Methylphenidate, amphetamines, and pemoline*
- 5.1.4 *Selegeline hydrochloride*
- 5.1.5 *Ritanserin*
- 5.1.6 *Reboxetine*

**5.2 Anticatataplectics**

- 5.2.1 *Sodium oxybate*
- 5.2.2 *Antidepressants*

**6.0 Discussion**

**7.0 Summary and Future Directions**

**1.0 INTRODUCTION**

Alertness is essential for overall well-being, and it impacts learning, performance and safety. Sustained alertness is especially important for individuals employed in high risk occupations and in areas involving public safety such as transportation, healthcare, the military, and law enforcement.<sup>1-6</sup> Individuals with sleep disorders associated with hypersomnia experience impaired alertness and decrements in performance across many areas of life.<sup>7-9</sup> Effective treatment of hypersomnia improves alertness and helps restore performance and productivity, improves quality of life, and decreases risk of injury to the individual and to others.<sup>10-14</sup>

Epidemiological studies of excessive sleepiness reveal wide variations in incidence and prevalence depending upon the populations studied. Excessive sleepiness is reported by approximately 10%-25% of the general population.<sup>15-19</sup> These figures emphasize the serious public health implications of untreated hypersomnia and the importance of clinical diagnosis and treatment of underlying sleep disorders that cause sleepiness.

Daytime sleepiness is defined by the International Classification of Sleep Disorders, Second Edition (ICSD-2)<sup>20</sup> as “the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep.” Excessive sleepiness varies in severity, and it becomes manifest most commonly during monotonous situations that require little interaction. Mild sleepiness can be overcome by activity or shift to a more stimulating activity. Severe sleepiness is characterized by an overwhelming need to sleep, unintended lapses into sleep, amnesia, and automatic behavior (the semiconscious continuation of activity while drowsy). Chronic pathological sleepiness is defined in the ICSD-2 as sleepiness that is present for at least three months prior to diagnosis.<sup>20</sup>

Recent advances in sleep medicine have increased our understanding of conditions associated with hypersomnia and have produced more options for treatment. In order to help physicians synthesize new information to support optimal clinical decision-making, the American Academy of Sleep Medicine (AASM) appointed a task force charged with reviewing available evidence regarding the treatment of narcolepsy and other hypersomnias of central origin. This paper updates the previous review paper on treatment of narcolepsy,<sup>21</sup> expands the scope of review to include other hypersomnias of central origin and provides a summary of

**Table 1**—Outline of the Hypersomnias of Central Origin not due to a Circadian Rhythm Sleep Disorder, Sleep Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep<sup>20</sup>

Narcolepsy with cataplexy
Narcolepsy without cataplexy
Narcolepsy due to medical condition
Narcolepsy, unspecified
Recurrent Hypersomnia
<i>Kleine-Levin Syndrome</i>
<i>Menstrual-related Hypersomnia</i>
Idiopathic Hypersomnia with Long Sleep Time
Idiopathic Hypersomnia without Long Sleep Time
Behaviorally Induced Insufficient Sleep Syndrome
Hypersomnia Due to Medical Condition
Hypersomnia Due to Drug or Substance
Hypersomnia Not Due to Substance or Known Physiological Condition (Nonorganic Hypersomnia, NOS)
Physiological (Organic) Hypersomnia, Unspecified (Organic Hypersomnia, NOS)

current evidence, including evidence grading using a standardized approach.

**1.1 Purpose**

The purpose of this paper is to summarize current knowledge about treatment of hypersomnias of central origin. The specific objectives are: 1) to provide a systematic and comprehensive review of the relevant medical literature regarding treatment of the hypersomnias, 2) to grade the evidence contained in the literature using the Oxford evidence grading system, 3) to discuss safety issues regarding use of medications for hypersomnia, and 4) to discuss the strengths and limitations of the available evidence. Findings from this paper will provide the foundation for development of evidence-based practice parameters by the Standards of Practice Committee (SPC) of the AASM.

**1.2 Causes of Excessive Sleepiness**

The most common cause of excessive daytime sleepiness (EDS) in modern society is probably due to some combination of insufficient sleep, inadequate sleep hygiene, and work schedules.<sup>19</sup> A variety of sleep disorders are associated with excessive daytime sleepiness. Examples include sleep-related breathing disorders, circadian rhythm sleep disorders, medication-induced sleepiness, periodic limb movement disorder, and sleepiness associated with insomnia.<sup>20</sup> Treatment of these underlying sleep disorders generally results in resolution or significant improvement in daytime sleepiness.

Individuals with hypersomnia of central origin usually experience daytime sleepiness despite an apparently adequate quantity of nocturnal sleep. The ICSD-2 organizes sleep disorders into eight categories based on a common complaint, a presumed basic etiology, or according to the organ system involved.<sup>20</sup> The sleep disorders contained within the Hypersomnias of Central Origin category are listed in Table 1. This category does not include circadian rhythm sleep disorders, sleep related breathing disorders, or other causes of disturbed nocturnal sleep. The scope of this review includes treatment of hypersomnia due to narcolepsy with cataplexy, narcolepsy without cataplexy, narcolepsy due to

**Table 2**—Summary of Hypersomnia Literature Search Strategy

**Inclusion criteria**

article deemed to be clinically relevant to topic, published within the acceptable time frame, does not meet an exclusion criterion

**Exclusion criteria**

editorials, letters to the editor, review papers, books and book chapters, abstracts from professional meetings, publications in languages other than English, studies involving non-human subjects, case reports with fewer than 10 subjects (adult narcolepsy topics) or fewer than 5 subjects (non-narcolepsy topics)

**Search dates**

- Narcolepsy and cataplexy: 1999 through April, 2006
- Non-narcolepsy topics: no start date limit through April, 2006
- Repeat (final) search: January, 2006 through October, 2006

**Table 3**—Summary of Safety Literature Search Strategy

General safety topics for the medications of interest were searched using the Physicians' Desk Reference<sup>31</sup> including adverse effects, pregnancy and breast-feeding issues, and pediatric issues. A specific search was performed to identify articles about individuals with sleep disorders who were receiving medications of interest.

**Medications of interest**

- Amphetamines and related preparations
- Methylphenidate and related preparations
- Modafinil
- Armodafinil
- Sodium oxybate
- Selegiline
- Reboxetine
- Selective serotonin reuptake inhibitors
- Tricyclic antidepressants
- Venlafaxine

medical conditions, narcolepsy unspecified, recurrent hypersomnia (Kleine-Levin syndrome and menstrual-related hypersomnia), idiopathic hypersomnia with long sleep time, idiopathic hypersomnia without long sleep time, and hypersomnia due to medical conditions. The decision was reached by the Standards of Practice Committee (SPC) to exclude treatment of behaviorally induced insufficient sleep syndrome, hypersomnia due to drugs or substances, hypersomnia not due to substances or known physiological conditions (nonorganic hypersomnia NOS) and physiological (organic) hypersomnia, unspecified, from consideration. The AASM Task Force Report on Use of Stimulants to Modify Performance during Sleep Loss<sup>22</sup> is a useful resource regarding treatment of the behaviorally induced insufficient sleep syndrome. The decision was reached by the SPC and the task force to exclude from consideration hypersomnia due to psychiatric disorders such as major depression, conversion or somatoform disorder, and seasonal affective disorder.

**Narcolepsy with cataplexy** is the most widely recognized and best characterized disorder in this category. Narcolepsy is characterized by excessive daytime sleepiness and inappropriate transition from wakefulness to REM sleep. Many of the features of narcolepsy, including cataplexy, hypnagogic hallucinations and sleep paralysis, are due to abnormal regulation of rapid eye movement (REM) sleep and dissociated REM sleep phenomena.<sup>20,23</sup> Disrupted nocturnal sleep may also be a prominent symptom. Current evidence strongly supports the pathogenic role of selective loss of hypocretin-containing neurons in the hypothalamus of individuals with narcolepsy with cataplexy.<sup>23-26</sup> Narcolepsy (with or without cataplexy) is a chronic and potentially disabling disorder that affects approximately 1 in 2000 individuals.<sup>27,28</sup>

**Narcolepsy without cataplexy** is characterized by excessive daytime sleepiness, naps which are typically refreshing, normal or moderately disturbed nocturnal sleep, and an abnormal tendency for inappropriate transition into REM sleep.<sup>20</sup> Cases of narcolepsy without cataplexy are thought to represent between 10% and 50% of all narcolepsy cases, but the precise incidence is not known.

**Narcolepsy due to a medical condition**, also known as secondary or symptomatic narcolepsy, is diagnosed when the direct cause of narcolepsy symptoms is a medical or neurological disorder.<sup>20</sup> In patients with sleep related breathing disorders (SRBD) plus hypersomnia of central origin and sleep-onset REM periods (SOREMPs) on the multiple sleep latency test (MSLT), this disorder should be diagnosed only if SOREMPs on the MSLT persist after adequate treatment of the SRBD. In addition, the hypersom-

nia is not better explained by another sleep disorder, mental disorder, medication use, or substance use disorder.

**Recurrent hypersomnia** is characterized by periodic hypersomnia episodes that last a few days to several weeks, and which recur weeks or months apart.<sup>20</sup> Cognitive and behavioral disturbances are common, including confusion, feelings of unreality, hallucinations, binge eating, hypersexuality, irritability and aggressive behavior. The best characterized form of recurrent hypersomnia is the Kleine-Levin syndrome, but other less well defined clinical subtypes have been described also. **Menstrual-related hypersomnia** occurs in association with the menstrual cycle, often within the first few months after menarche.<sup>20</sup>

**Idiopathic hypersomnia with long sleep time** is characterized by excessive sleepiness with prolonged and unrefreshing naps of up to three or four hours. The major sleep time is prolonged (at least 10 hours and often 12-14 hours) with few or no awakenings. Patients with idiopathic **hypersomnia without long sleep time** experience chronic daytime sleepiness and the major sleep episode is either normal in duration or slightly prolonged (less than 10 hours).<sup>20</sup>

**Hypersomnia due to medical condition** is characterized by hypersomnia secondary to a coexisting medical or neurological disorder that causes hypersomnia. A variety of medical and neurological conditions are associated with hypersomnia, including Parkinson disease and other neurodegenerative conditions, head trauma, stroke, encephalitis, inflammatory conditions, metabolic and toxic conditions, tumors and other lesions of the central nervous system, and genetic disorders. Examples of genetic disorders associated with hypersomnia include myotonic dystrophy, Prader-Willi syndrome, Niemann Pick type C disease, and fragile X syndrome.<sup>20</sup>

Patients with Parkinson disease and hypersomnia may be a challenge to classify. When patients with Parkinson disease experience hypersomnia due to insufficient sleep (due to suboptimal control of symptoms), the diagnosis should be insomnia due to medical condition. When the hypersomnia is caused by side effects of dopaminergic agents, the diagnosis should be hypersomnia due to drug or substance. When hypersomnia is of central origin and the patient does not meet criteria for narcolepsy due to medical condition, the diagnosis is hypersomnia due to medical condition.<sup>20</sup>

## 2.0 BACKGROUND

The AASM (formerly the American Sleep Disorders Association) first sponsored a review paper on narcolepsy and its treatment with stimulants in 1994.<sup>29</sup> This paper helped form the basis for the first comprehensive practice parameters for use of stimulants in the treatment of narcolepsy.<sup>30</sup> The review paper addressed appropriate medication doses, development of tolerance, potential for side effects, adverse reactions and abuse, and medication use in children and pregnant or breast-feeding women. The second review and practice parameters were published by the AASM in 2001.<sup>21</sup> This paper provided updated and expanded evidence-based recommendations, including coverage of medications used for treatment of cataplexy, therapeutic use of scheduled naps, driving and quality of life issues, toxicity and side effect issues, pregnancy and nursing issues, and consideration of relative cost of medications.

In the six years since publication of the 2001 paper, several new developments have occurred that are relevant to this topic: 1) availability of newer pharmacologic agents for treatment of hypersomnia and cataplexy, 2) expansion of the medical literature regarding treatment of hypersomnia with medications and behavioral interventions, and 3) creation of the ICSD-2, which formalized the concept of grouping the hypersomnias of central origin not due to a circadian rhythm sleep disorder, sleep related breathing disorder, or other cause of disturbed nocturnal sleep, and created diagnostic criteria for each entity.

The SPC decided to align evidence reviews and practice parameters with the organizational structure of the ICSD-2 whenever possible. For this reason the scope of this review has been expanded beyond narcolepsy to include treatment of other hypersomnias of central origin, as discussed above.

In 2006 the SPC established the Treatment of Hypersomnia task force and identified SPC liaisons. The task force conducted its work through a combination of regularly scheduled telephone conference calls, one face-to-face meeting in June, 2006, numerous email communications, and through use of a web-based directory and an electronic forum developed by the AASM.

## 3.0 METHODS

The SPC developed a list of specific questions and issues to be addressed in the review. This resulted in creation of Population, Intervention, Comparison, and Outcome (PICO) tables, which were used to guide the task force and to focus the review process on clinically relevant issues. The PICO tables for this project are available on the AASM website directory at [www.aasmnet.org](http://www.aasmnet.org). The task force reviewed prior AASM publications relevant to this topic.

### 3.1 Literature Search Strategy

The task force developed search terms and search strategies suitable for queries of the medical literature using Medline. Explicit inclusion and exclusion criteria were established to guide selection of relevant citations. Inclusion and exclusion criteria, publication dates, and other limitations of the searches are summarized in Table 2. Search terms included the names of each disorder and each medication of interest. Editorials, letters to the editor, books and book chapters, abstracts from professional meetings, review articles, publications in languages other than English, and

**Table 4**—Oxford Centre Evidence-Based Medicine Levels of Evidence<sup>32</sup> (Abbreviated; full table available on AASM website at [aasmnet.org](http://aasmnet.org))

Evidence Level	Study Design or Description
I	Randomized controlled trial (RCT) with narrow confidence intervals
II	Randomized trials without narrow confidence intervals, or with methodological problems, or cohort studies of low quality
III	Nonrandomized concurrently controlled studies or case-control studies
IV	Case-control or cohort studies with methodological problems, or case series
V	Expert opinion, or studies based on physiology or bench research

studies involving non-human subjects were excluded.

Searches involving narcolepsy and cataplexy were performed for the period from 1999 through April 26, 2006, since the search performed for the previous treatment of narcolepsy paper in 2001 included citations through 2000. Searches involving non-narcolepsy topics were performed on April 28, 2006 with no date limit, since non-narcolepsy topics were not covered in the previous papers. A second and final search using the same search strategy was performed in October, 2006 in order to identify new articles published after the initial search.

A separate search was performed to query the medical literature with regard to medication safety issues, including adverse effects, pregnancy and breast-feeding issues, and pediatric issues. This search involved a dual strategy in which the Physicians' Desk Reference<sup>31</sup> was used to identify general information about the medications of interest without regard to diagnosis. Second, the task force performed a more specific Medline search to identify articles regarding individuals who received the medications of interest, and the majority of these reports involved subjects with sleep disorders. In contrast to the strategy employed for the literature search regarding treatment a less restrictive approach was utilized, allowing for review of case reports and articles with small numbers of subjects. Our review also included all treatment articles extracted above that reported adverse events. Extractions were performed on articles that were otherwise excluded from consideration for the regular review, including those that addressed hypersomnia and fatigue in the setting of psychiatric illness and other medical conditions. The Safety search strategy is summarized in Table 3.

The initial Medline search performed on April 26, 2006, yielded 1073 citations. Task force members reviewed each citation by title and abstract to ascertain whether the article was relevant and whether inclusion or exclusion criteria were met. Additional articles were considered for inclusion by searching the bibliographies of previously identified articles (a process known as pearl-ing). The task force accepted thirty-three treatment articles for review and the remainder were rejected because the article was deemed not relevant (did not address issues in the PICO tables) or because the article contained exclusionary features. The task force identified 48 articles for the Safety search; this group includes all medication-related articles from the treatment search.

## 3.2 Evidence Review

Relevant articles that met inclusion criteria were obtained by the AASM and the full length article was made available to members of the task force using a website directory. The task force developed data extraction forms customized for this project and these forms were used to record and summarize key findings from each article identified. The task force piloted the data extraction forms on a subset of articles to identify problems with the format or content of the forms, and appropriate revisions were made.

Review of the articles and completion of the data extraction forms were performed in a two step process. Primary reviewers (individuals with doctoral level education) were identified and trained by the AASM using a standardized training module regarding use of evidence-based medicine techniques for data extraction and evidence grading. Following the initial review and data extraction process, members of the task force (secondary reviewers) reviewed each citation and data extraction form, and made corrections when necessary. Discrepancies between the primary and secondary reviewers were discussed and resolved by the task force chairman. This process is identical to that used by the AASM Standards of Practice Committee and sponsored task forces for reviewing and grading medical evidence. The task force used the Oxford Centre for Evidence-based Medicine Levels of Evidence<sup>32</sup> in order to grade the strength of evidence for each citation. This system for evidence grading is summarized in Table 4. Evidence grading was not performed for those extractions used solely for assessing adverse effects of the medications of interest.

An Evidence Table—Table 5—was developed to summarize key findings from each citation. Information extracted from the safety review is provided in Table 6 and general safety information from the Physicians' Desk Reference<sup>31</sup> is provided in Table 7. Tables 5 and 6 are available online at [www.aasmnet.org](http://www.aasmnet.org) appended to the end of this review in PDF format. All statements that indicate significant changes in measurements mean statistically significant differences exist, unless stated otherwise in the text or Evidence Table.

After completion of literature review, data extraction, and evidence grading, the task force developed successive drafts of the review paper through a series of communications via conference calls and e-mail correspondence. The review paper was produced in consultation with the SPC liaisons, and with commentary by outside reviewers with expertise in this field. The paper was revised to incorporate comments from each reviewer. The final document was reviewed and approved by the SPC, and by the Board of Directors of the AASM.

## 4.0 RESULTS

### 4.1 Treatment of Hypersomnia due to Narcolepsy with or without Cataplexy

#### 4.1.1 Medications

##### 4.1.1.1 Amphetamine, Methamphetamine, Dextroamphetamine, Methylphenidate, and Related Preparations

The traditional stimulants are considered mainstays for treatment of sleepiness associated with narcolepsy.<sup>21</sup> The previous practice parameters published in 2001 by the AASM identified three level 2 studies and four level 5 studies that support the ef-

ficacy of traditional stimulants for treatment of sleepiness in narcolepsy.<sup>21</sup> Our updated search from 1999 through October, 2006 identified no new studies of traditional stimulants for this indication that met inclusion criteria.

#### 4.1.1.2 Modafinil and Armodafinil

Modafinil is a non-amphetamine wakefulness-promoting medication, and armodafinil is the (R)- enantiomer of modafinil with a longer half-life. Our search regarding treatment of sleepiness in patients with narcolepsy using modafinil or armodafinil identified 14 articles. Four studies provide level 1 evidence, two provide level 2 evidence, and seven provide level 3 or 4 evidence regarding the efficacy of modafinil for treatment of sleepiness associated with narcolepsy. One study involving armodafinil provided level 1 evidence.

The study by Black et al.<sup>33</sup> involved subjects with narcolepsy who received modafinil for treatment of excessive sleepiness due to narcolepsy. After completing a two week single-blind phase in which subjects received their usual doses of modafinil, subjects were randomized into four groups: modafinil placebo plus sodium oxybate placebo (placebo group), modafinil placebo plus sodium oxybate (sodium oxybate group), modafinil plus sodium oxybate placebo (modafinil group), and modafinil plus sodium oxybate (sodium oxybate/modafinil group). The primary efficacy measure was the mean sleep latency on the 20-minute Maintenance of Wakefulness Test (MWT), and secondary measures included the Epworth Sleepiness Scale (ESS), diary recordings, and the Clinical Global Impression-change scale. The modafinil group displayed an average mean sleep latency of 9.86 minutes, which represents a significant difference compared with the placebo group (6.87 minutes). Also, when subjects were transitioned from their baseline modafinil dosages to the placebo group, the average mean sleep latency decreased from 9.74 minutes to 6.87 minutes. This finding is also consistent with therapeutic effect from modafinil. However, ESS scores were not significantly different between the placebo and modafinil groups. Findings also demonstrated improvement in objective and subjective sleepiness as measured by the MWT and ESS in subjects who received modafinil plus sodium oxybate, which indicates evidence of an additive effect of modafinil and sodium oxybate.

The level I study by Schwartz et al.<sup>34</sup> is a double-blind, randomized controlled trial comparing single daily dose treatment (modafinil 200 mg or 400 mg in the morning) versus a multi-dose strategy (200 mg twice per day or 400 mg plus 200 mg). There was improvement in daytime alertness as measured by the MWT in all intervention groups compared to baseline, and subjects who received a split dose composed of modafinil 200 mg or 400 mg in the morning plus 200 mg at midday experienced more alertness than subjects who received only 200 mg in the morning. Although results support the conclusion that a split dose strategy is associated with better control of daytime sleepiness than a single daily dose in patients with residual afternoon or evening sleepiness, this study does not provide information supporting the efficacy of modafinil for treatment of excessive sleepiness compared with placebo or traditional stimulants. In a level 1 double-blind, randomized trial by Schwartz et al.<sup>35</sup> comparing a single daily dose of modafinil 400 mg per day with a split dose of 400 mg plus 200 mg, subjects in the latter group experienced improvement in objective and subjective sleepiness in the afternoon and eve-

**Table 7**—General Medication Information and Key Safety Issues

<b>Medication</b>	<b>Usual daily dose</b>	<b>FDA Prenancy Category</b>	<b>Breastfeeding Issues</b>	<b>Pediatric Issues</b>	<b>Contraindications</b>	<b>Special Comments</b>
Amphetamine (Adderall)	5-60 mg	C	Drug excreted in milk; rec no breast feeding	Not recommended in pts < 3 years	Not recommended for children with known structural cardiac defects; contraindicated in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, h/o drug abuse, during or within 14 days of administration of MAO inhibitors	“Black box warning” regarding high potential for abuse
Methyphenidate (Ritalin)	20-40 mg in adults; 5-20 mg in children	C	Excretion not well characterized; exercise caution with BF	Not recommended in pts < 6 years; some data suggest slowing of growth rate; height and weight should be monitored in children	Use with caution in pts with h/o drug dependence; pts being considered for treatment should have a careful cardiac history and physical exam to assess for the presence of cardiac disease	
Modafinil	100-400 mg	C	Excretion in milk not characterized; exercise caution with BF	Pediatric use not systematically studied		Generally low abuse potential; Schedule IV Controlled Substances
Sodium oxybate	4.5-9 g per night	B	Excretion in milk not characterized; exercise caution with BF	Safety and effectiveness in pts < 16 years of age not established		“Black box” warning regarding abuse potential; should not be used with alcohol or other CNS depressants
Selegiline	5-10 mg	C	Excretion in milk not characterized; exercise caution with BF	safety and effectiveness in children not established		MAO inhibitor; use with caution
Fluoxetine	10-40 mg	C	Excreted in milk; nursing not recommended	Safety and effectiveness assessed in children aged 8-18 yrs with major depressive disorder and 7-18 yrs with OCD		“Black box” warning regarding increased risk of suicidal thinking and behavior in short term studies of children and adolescents with major depressive disorder and other psychiatric disorders; families should be advised of the need for close observation and communication with the prescriber; avoid abrupt discontinuation of drug due to possible adverse events
Venlafaxine	75-375 mg	C	Excreted in milk; requires individualized decision regarding nursing	Safety and effectiveness not established in children	Co-administration with MAO inhibitors is contraindicated	“Black box” warning regarding increased risk of suicidal thinking and behavior in short term studies of children and adolescents with major depressive disorder and other psychiatric disorders; families should be advised of the need for close observation
Protriptyline	10 mg	Not established	Excretion in milk not known	Safety and effectiveness not established in children		

ning compared with subjects who received 400 mg per day in a single dose. Subjects who received the split dose also exhibited improvements in executive function compared with those who received a single daily dose. The level 1 study by Schwartz<sup>36</sup> is a double-blind, placebo-controlled study that assessed subjects previously exposed to modafinil who reported dissatisfaction with late afternoon or evening sleepiness. Subjects who received 400 mg per day in a divided dosage experienced improvement in subjective and objective measures of sleepiness in the afternoon or evening compared with those on a single dosage.

Level 1 evidence was presented by Harsh et al. in a large, multicenter double-blind, randomized controlled trial of armodafinil.<sup>37</sup> Subjects who received 150 mg or 250 mg as a single dose experienced improvement in subjective and objective sleepiness compared with placebo during the 12 week trial. Efficacy was assessed with the MWT using six 20-minute tests, the Clinical Global Impression of Change (CGI-C), the ESS, patient diaries, and evaluation of cognitive performance and fatigue. Compared with baseline measurements, subjects experienced an average change in mean sleep latency on the MWT of 1.3, 2.6, and 1.9 minutes in the 150 mg, 250 mg, and combined groups, respectively, compared with a decrease of 1.9 minutes for placebo ( $P < 0.01$ ). These measurements involved MWT tests at 09:00-15:00. Late-day MWT scores (15:00-19:00) also improved significantly in both treatment groups compared with placebo (2.8 minute improvement in combined group versus placebo). Although subjects who received armodafinil showed evidence of sustained improvements in alertness across the entire day, this study did not provide a direct comparison of modafinil and armodafinil.

In a study with level 2 evidence,<sup>38</sup> narcolepsy patients were compared with control subjects in a three-week titration of modafinil (200 mg, 300 mg, and 400 mg) versus placebo. Changes in alertness were assessed using the ESS (decrease in median score from 14.5 to 12.5) and the MSLT (mean sleep latency change from 3.2 min to 6.6 min) following introduction of modafinil. The primary objective in this study was assessment of changes in low resolution brain electromagnetic tomography (LORETA) to identify brain regions associated with vigilance in controls and subjects with narcolepsy, and not assessment of response to treatment with modafinil. In a study with level 2 evidence,<sup>39</sup> subjects who had participated in a 16-week open label study with modafinil entered a two-week randomized placebo-controlled trial to evaluate continued efficacy and safety of modafinil. There was sustained improvement in subjective and objective sleepiness in subjects receiving modafinil (200-500 mg per day), with return of excessive sleepiness in subjects who received placebo.

A level 3 study by Guilleminault et al.<sup>40</sup> evaluated the response of 60 subjects with narcolepsy with cataplexy who were begun on treatment with modafinil in an open label study. The trial included four groups of patients: 1) drug naïve subjects, 2) subjects who were previously treated with traditional stimulants, 3) subjects who were previously treated with anti-cataplexy medication, and 4) subjects treated with stimulants and anti-cataplexy medication. Subjects were treated with modafinil at a dosage of 100 to 600 mg per day and clinical response was assessed using the ESS and a visual analog scale of subjective sleepiness. Drug naïve subjects demonstrated the best clinical response to modafinil, while patients treated previously with traditional stimulants experienced the most difficulty with transition to modafinil. Eight of 14 subjects requested a return to traditional stimulants.

A small open label study with level 4 evidence reported by Ivanenko et al.<sup>41</sup> provides data regarding response to modafinil in children with sleepiness due to narcolepsy or idiopathic hypersomnia. The study assessed the effects of modafinil on daytime sleepiness, mood, and academic performance in 13 children (mean age  $11.0 \pm 5.3$  yrs) with narcolepsy or idiopathic hypersomnia. Treatment with modafinil was associated with subjective improvement in sleepiness as reported by parents, and objective improvement as measured by the MSLT ( $6.6 \pm 3.7$  min at baseline versus  $10.2 \pm 4.8$  min on modafinil). The children also showed improvement in mood and academic performance, and modafinil was generally well tolerated.

A large multicenter open label study with level 4 evidence<sup>42</sup> compared the efficacy and safety of modafinil in narcolepsy patients previously treated with stimulant medications following a two-week “washout” period. Treatment with modafinil 200 mg or 400 mg was associated with significant subjective improvement in daytime alertness versus baseline (no medication), regardless of which stimulant was taken prior to administration of modafinil. Treatment benefit was maintained throughout six weeks of treatment.

An open label study with level 4 evidence by Becker et al.<sup>43</sup> assessed changes in fatigue, mood, and health-related quality of life in narcolepsy patients. After a 14-day “washout” period, subjects received 200-400 mg of modafinil per day (>70% received 400 mg per day) during a six-week trial. Treatment with modafinil was associated with improvement in health-related quality of life using the SF-36 and improved mood using the Profile of Mood States (POMS) in comparison with no medication treatment. Inclusion criteria for this study included patient dissatisfaction with traditional stimulants.

A novel study by Dauvilliers et al.<sup>44</sup> compared subjective response to modafinil in men and women with narcolepsy, including subjects with catechol-O-methyltransferase (COMT) gene sexual dimorphism. Results indicate that COMT genotype distribution between men and women with narcolepsy is associated with response to modafinil. The optimal daily dose of modafinil was lower in subjects with low activity COMT genotype, and optimal daily dose was approximately 100 mg lower in women than men. Ninety-one percent of subjects experienced a moderate to good response to modafinil as measured by the Global Clinical Impression Scale.

A long-term (40 week) open label trial with level 4 evidence by Mitler et al.<sup>45</sup> assessed the efficacy and safety of modafinil in subjects who were studied previously in two double-blind placebo-controlled studies. Subjects received modafinil 200 mg to 400 mg per day (approximately 75% received 400 mg per day). Subjects demonstrated sustained subjective improvement in excessive sleepiness as measured by the ESS and quality of life measures, and modafinil was generally well tolerated across the period of study.

#### **4.1.1.3 Sodium Oxybate**

Sodium oxybate is a rapidly acting sedative/hypnotic medication. Our search identified three studies with level 1 evidence, and two studies with level 4 evidence regarding the effectiveness of sodium oxybate for treatment of sleepiness associated with narcolepsy. We identified several older studies that reported clinical trials using a related drug, gammahydroxybutyrate (GHB). The

GHB studies were not reviewed because sodium oxybate, which is the sodium salt of GHB, is the only regulated and marketed form of GHB in the United States.

In a large placebo-controlled randomized trial with level 1 evidence,<sup>46</sup> sodium oxybate was evaluated using 3 g, 6 g, and 9 g per night in a divided dosage. Subjective sleepiness was improved at 6 g and 9 g doses as measured by the ESS and by reduction in the number of inadvertent naps or sleep attacks, with the greatest improvement at the 9 g/night dose. This study involved 136 subjects with narcolepsy with cataplexy who were allowed to continue receiving stable doses of stimulant medications. In a level 1 study<sup>47</sup> that involved a large double-blind, placebo-controlled trial of sodium oxybate at 4.5-9 g/night, subjective (ESS) and objective (MWT) measures of sleepiness were improved in a dose-related fashion. Subjects were allowed to continue use of traditional stimulants at a stable dosage.

The study by Black et al.<sup>33</sup> involved subjects with narcolepsy who previously received modafinil for treatment of excessive sleepiness due to narcolepsy. Results from this study were reviewed previously in Section 4.1.1.2 (modafinil and armodafinil). Following a two-week single-blind baseline phase during which they received their customary dosage of modafinil (200 mg to 600 mg per day), subjects were randomized into four groups: modafinil placebo plus sodium oxybate placebo (placebo group), modafinil placebo plus sodium oxybate (sodium oxybate group), modafinil plus sodium oxybate placebo (modafinil group), and modafinil plus sodium oxybate (modafinil/sodium oxybate group). After eight weeks of treatment, findings indicated improvement in objective (MWT) and subjective sleepiness (ESS) in the sodium oxybate group compared with the placebo group. The average mean sleep latency on MWT for the placebo group was 6.87 minutes compared with 11.97 minutes in the sodium oxybate group ( $P < 0.001$ ), and 13.15 minutes in the combined sodium oxybate/modafinil group ( $P < 0.001$ ). This latter finding is consistent with an additive effect in subjects who received both modafinil and sodium oxybate. This paper represents the only study identified that allows comparison between subjects with narcolepsy who received sodium oxybate versus modafinil. In this study, the degree of improvement in alertness as measured by the MWT is greater in the sodium oxybate group than in the modafinil group (average mean sleep latency 11.97 minutes for sodium oxybate; 9.86 minutes for modafinil group; 6.87 minutes for placebo group). Subjective sleepiness as measured by the ESS after eight weeks of treatment also demonstrated greater improvement in the sodium oxybate group than the modafinil group or the placebo group (ESS 12.0 for sodium oxybate group; 15.0 for modafinil group; 16.0 for placebo group). The difference between sodium oxybate and placebo was statistically significant ( $P < 0.001$ ), whereas the difference between modafinil and placebo was not ( $P < 0.767$ ).

A small open-label pilot study with level IV evidence was reported by Mamelak et al.<sup>48</sup> in which subjects with narcolepsy with cataplexy were given 4.5 g, 6 g, 7.5 g, and 9 g of sodium oxybate in a divided dosage at night. Subjects demonstrated improvements in subjective (ESS) and objective (MWT) measures of sleepiness. A 12-month, open-label extension trial with level 4 evidence<sup>49</sup> demonstrated improvement in subjective sleepiness as measured by the ESS following administration of 3-9 g per night of sodium oxybate.

#### **4.1.1.4 Selegiline**

Selegiline is an MAO-B inhibitor that is metabolized to amphetamine and methylamphetamine. Our search identified no studies that met inclusion criteria regarding treatment of sleepiness due to narcolepsy with selegiline. The previous AASM practice parameters paper on treatment of narcolepsy identified two level 2 studies and one level 4 study which provided limited evidence of effective treatment of hypersomnia associated with narcolepsy using selegiline.

#### **4.1.1.5 Reboxetine**

Our search identified one small open-label study with level 4 evidence regarding treatment of sleepiness and cataplexy associated with narcolepsy using reboxetine, a new selective noradrenaline reuptake inhibitor with antidepressant efficacy.<sup>50</sup> This preliminary study suggests that reboxetine exerts stimulant and anti-cataplectic effects in narcolepsy patients. Subjective (ESS) and objective (MSLT) measures of sleepiness were employed. Following treatment for two weeks, a significant improvement in daytime sleepiness was observed as measured by a mean decrease of 48.6% on the ESS, and a mean increase of 54.7% in sleep latency on the MSLT.

#### **4.1.1.6 Ritanserin**

We identified two papers with level 2 evidence that assessed the effectiveness of ritanserin, a 5-HT<sub>2</sub> antagonist, for treatment of excessive sleepiness associated with narcolepsy. The study by Lammers et al.<sup>51</sup> was a double-blind, placebo-controlled trial involving 28 subjects with narcolepsy. Ritanserin 5 mg per day was added to the subjects' usual medication during a four-week trial. There was improvement in subjective daytime sleepiness but no significant change in mean sleep latency was demonstrated on the MSLT. A second study by Mayer et al.<sup>52</sup> reported results from a double-blind, placebo-controlled study in which 134 subjects with narcolepsy received ritanserin 5 mg or 10 mg, or placebo in addition to their usual medication regimes. This study showed some improvement in subjective quality of sleep, but in contrast to the previous study, there was no significant improvement in daytime alertness as measured by a 40-hour polygraphic recording performed at baseline and after four weeks of treatment.

#### **4.1.1.7 Pemoline**

Pemoline was identified as an effective option for treatment of sleepiness associated with narcolepsy in the AASM 2001 practice parameters paper.<sup>21</sup> However, the rare but potentially fatal hepatic toxicity associated with pemoline has severely limited clinical use of this medication, and pemoline is no longer being produced in the United States. Our updated search revealed no new studies regarding use of pemoline for treatment of sleepiness in narcolepsy.

### **4.1.2 Scheduled Naps Plus Stimulants Versus Stimulants Alone**

Previous AASM papers have indicated that scheduled naps can be beneficial to combat sleepiness associated with narcolepsy, but naps are seldom effective as a primary therapy.<sup>21</sup> Our updated

search identified one level 2 study by Rogers et al.<sup>53</sup> that compared three different sleep schedules for reducing daytime sleepiness in narcolepsy. In 29 subjects with narcolepsy receiving treatment with medication, the addition of two 15-minute naps did not alter the severity of daytime sleepiness or the duration of unscheduled daytime sleep. The combination of scheduled naps and regular nocturnal sleep times produced significant reduction in severity of sleepiness and duration of daytime sleep in treated narcoleptics. The authors conclude that scheduled sleep periods are helpful only for those narcolepsy patients who remain profoundly sleepy despite treatment with stimulant medications.

## **4.2 Treatment of Cataplexy**

### **4.2.1 Sodium Oxybate**

Our search identified four studies that examined the effectiveness of sodium oxybate for treatment of cataplexy. One level 1 study<sup>54</sup> reported results of a large randomized double-blind, placebo-controlled trial of sodium oxybate using 4.5 g, 6 g, 7.5 g, and 9 g/night doses. Significant dose-dependent reductions in cataplexy were reported for 4.5 g, 6 g, and 9 g doses, with reductions in median number of cataplectic attacks of 57%, 65%, and 87.7%, respectively, compared with placebo. Another study with level 1 evidence reported significant improvement in cataplexy frequency at a dosage of 9 g/night only compared with placebo.<sup>46</sup> A level 1 study<sup>55</sup> reported results from a double-blind controlled trial with abrupt discontinuation of sodium oxybate during a two week period with continuation of subjects' usual stimulant medication. Subjects experienced a median increase of 21 cataplexy attacks during the withdrawal period compared to subjects who continued to receive medication. An open-label 12-month study with level 4 evidence<sup>48</sup> demonstrated sustained reduction of cataplexy frequency over the period of study when subjects received sodium oxybate doses of 3 to 9 g per night.

### **4.2.2 Medications other than sodium oxybate**

In the previous AASM practice parameters paper on treatment of narcolepsy,<sup>21</sup> a recommendation was included indicating that tricyclic antidepressants and fluoxetine may be effective treatment for cataplexy (Guideline). The recommendation for tricyclic antidepressants was based on a single level 5 study as well as clinical experience and committee consensus. The recommendation for fluoxetine was based on one level 2 and one level 5 study.

Our review identified only two additional studies involving treatment of cataplexy with medications other than sodium oxybate published since 2000 which met inclusion criteria. Lammers et al.<sup>51</sup> reported results from a double-blind controlled trial with level 2 evidence using ritanserin, a long acting 5-HT<sub>2</sub> receptor blocker. Subjects received 5 mg per day of ritanserin or placebo plus their usual medications for narcolepsy. There was no significant change in the frequency of cataplexy in subjects who received ritanserin. In an open-label study with level 4 evidence, Larrosa et al.<sup>50</sup> evaluated 12 subjects with narcolepsy with cataplexy treated with reboxetine, a selective norepinephrine reuptake inhibitor with demonstrated antidepressant effects. In this brief study, subjects were assessed before and two weeks after initiation of treatment, and a significant reduction in the cataplexy subscore of the Ullanlinna Narcolepsy Scale was present.<sup>50</sup>

The paucity of formal clinical trials involving treatment of cataplexy may reflect, at least in part, the widespread "off-label" clinical use of antidepressants for treating cataplexy. The literature regarding treatment of cataplexy consists primarily of case reports and small open-label studies. A paper by Houghton et al.,<sup>56</sup> provides a review of the medical treatment options for cataplexy.

## **4.3 Treatment of Disrupted Nocturnal Sleep Associated with Narcolepsy**

### **4.3.1 Sodium Oxybate**

Sodium oxybate was associated with improved sleep architecture in two studies, including a reduction in nocturnal awakenings.<sup>46,48</sup> One level 4 study reported a subjective decrease in nocturnal awakenings at 7.5 and 9 g/night doses,<sup>48</sup> while the second study with level 1 evidence reported this finding at the 9 g/night dose only.<sup>46</sup> Sodium oxybate was associated with increased nighttime delta sleep in a dose-dependent manner in the study by Mamelak et al.<sup>48</sup>

### **4.3.2 Hypnotic Medications**

Our review yielded no studies that met inclusion criteria using traditional hypnotic medications for treatment of disrupted nocturnal sleep associated with narcolepsy.

## **4.4 Treatment of Hypnagogic Hallucinations and Sleep Paralysis in Patients with Narcolepsy**

### **4.4.1 Sodium Oxybate**

We identified two studies that provide data on the effects of sodium oxybate on self-reported incidence of hypnagogic hallucinations (HH) and sleep paralysis (SP).<sup>46,48</sup> In one study, when subjects with narcolepsy received 4.5 to 9 g per night doses, the proportion of patients reporting a decrease in HH ranged from 29%-76%, and the proportion of patients reporting a decrease in SP ranged from 38%-76%.<sup>48</sup> However, the second study<sup>46</sup> with sodium oxybate revealed no significant differences in HH and SP when compared with placebo.

### **4.4.2 Antidepressant Medications**

Our review identified no studies that reported changes in hypnagogic hallucinations or sleep paralysis in association with antidepressant medications.

## **4.5 Studies with Quality of Life Data**

We identified three studies that provide information regarding changes in quality of life measures in response to treatment with medication.<sup>14,43,45</sup> Two studies involve treatment with modafinil,<sup>43,45</sup> and one study involves sodium oxybate.<sup>14</sup> The study by Weaver et al.<sup>14</sup> was designed to assess changes in functional status following treatment with sodium oxybate. There was significant improvement in functional status as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ) in subjects who received 6 and 9 g per night of sodium oxybate compared with placebo. The study by Mitler et al.<sup>45</sup> showed improvement in

quality of life scores in six of eight domains following treatment with modafinil. In the study by Becker et al.<sup>43</sup> there was significant improvement in functional status as measured by the SF-36 instrument in subjects treated with modafinil.

#### **4.6 Treatment of Hypersomnia Associated with Narcolepsy due to Medical Conditions**

Our search identified no studies that met inclusion criteria regarding treatment of hypersomnia associated with narcolepsy due to medical conditions.

#### **4.7 Treatment of hypersomnia due to Recurrent Hypersomnia**

Our search identified one small case series with level 4 evidence involving five adolescents with Kleine-Levin syndrome treated with lithium carbonate.<sup>57</sup> Although all patients experienced relapses while receiving lithium carbonate, the duration of hypersomnia episodes was shorter and there were no behavioral symptoms during episodes in which subjects were treated with lithium carbonate. Several small case reports indicate varying degrees of improvement or lack of improvement associated with treatment with a variety of medications including stimulants, anti-epileptic medications, antidepressants, and neuroleptics. A systematic review of Kleine-Levin syndrome patients by Arnulf, et al.<sup>58</sup> reports that sleepiness decreased in 40% of 75 treated patients, using stimulants (primarily amphetamines). We identified no controlled studies that report results of treatment of recurrent hypersomnia with medications.

#### **4.8 Treatment of Hypersomnia due to Idiopathic Hypersomnia**

Our search identified one study<sup>59</sup> that met inclusion criteria involving treatment of idiopathic hypersomnia with or without long sleep time. This small open-label level 4 study included 18 subjects with idiopathic hypersomnia and 24 subjects with narcolepsy. Following treatment with modafinil at 200 to 500 mg/day in two divided doses, subjects with idiopathic hypersomnia experienced a significant improvement in subjective drowsiness and number of sleep attacks per day. The small open-label study by Ivenenko<sup>41</sup> involving treatment of 13 children with modafinil includes three children with idiopathic hypersomnia and 10 children with narcolepsy. The small sample size of subjects with idiopathic hypersomnia makes it difficult to draw conclusions regarding modafinil treatment for idiopathic hypersomnia in children. Anecdotal clinical experience with treatment of idiopathic hypersomnia with traditional stimulants has suggested variable and often only modest improvement in sleepiness.<sup>60</sup> A variety of other medications have been prescribed for treatment of idiopathic hypersomnia, including antidepressants, clonidine, levodopa, bromocriptine, selegiline, and amantadine.<sup>60</sup> However, there are no reports that describe a consistent response to these medications for this condition.

#### **4.9 Treatment of Hypersomnia due to Medical Conditions**

Our search revealed seven studies related to the treatment of hypersomnia due to medical conditions<sup>61-67</sup>: three studies involve Parkinson disease, two involve multiple sclerosis (MS), and two involve myotonic dystrophy. All but one of these studies investigated the impact of modafinil on EDS in these conditions.

Hogl et al.<sup>61</sup> performed a double-blind, placebo-controlled crossover study (level 2 evidence) involving modafinil for treatment of sleepiness in 12 PD subjects. Subjects were given modafinil 100 mg/day during week 1 and 200 mg/day during week 2. There was improvement in subjective sleepiness as measured by the ESS, but no significant improvement was demonstrated in objective sleepiness as measured by the MWT. A small four week open-label study with level 4 evidence involving modafinil in PD (10 subjects) demonstrated similar subjective improvement in EDS as measured by the ESS.<sup>62</sup> Ondo et al.<sup>63</sup> performed a randomized, double-blind, placebo-controlled trial with level 2 evidence involving modafinil (200 mg or 400 mg/day) in 40 subjects with PD. In contrast to the previous findings, there were no somnolytic effects associated with modafinil using objective (MSLT) or subjective (ESS) measures of sleepiness. The Unified Parkinson's Disease Rating Scale showed no significant changes with modafinil in the Ondo or the Nieves studies.

Rammohan et al.<sup>64</sup> performed a single-blind, placebo-controlled pilot study of modafinil for treatment of fatigue and sleepiness in 72 subjects with MS (level 2 evidence). Subjects were given modafinil (200 and 400 mg/day) or placebo, and assessments using the ESS and several fatigue measures revealed improvement in sleepiness at both doses, but interestingly, fatigue improved only with 200 mg/day. An open-label study with level 4 evidence involving 50 subjects with MS given up to 300 mg/day of modafinil demonstrated improvement in sleepiness and fatigue based on self-reports.<sup>65</sup>

Talbot et al.<sup>66</sup> reported results of a randomized, double-blind, placebo-controlled crossover study involving 20 subjects with myotonic dystrophy who were given modafinil. This study provided level 1 evidence. Following four weeks of treatment, improvement in sleepiness was evident as measured by prolongation of the mean sleep latency on the MWT. There was a nonsignificant reduction in subjective sleepiness using the ESS. A small open-label study with level 4 evidence involving methylphenidate for treatment of sleepiness associated with myotonic dystrophy demonstrated improvement in subjective sleepiness in 7 of 11 subjects at doses up to 40 mg/day. Two subjects developed signs of tolerance at the maximum dose.<sup>67</sup>

#### **4.10 Comprehensive Management Approach for Narcolepsy and other Hypersomnias**

Previous AASM review papers and practice parameters have emphasized the importance of providing a comprehensive approach to management of narcolepsy.<sup>21</sup> General strategies include patient and family education, counseling regarding the importance of good sleep hygiene and medication compliance, discussion of safety issues including driving recommendations individualized for each patient's circumstances, discussion of potential adverse side effects of medication, and vocational counseling. Regular follow-up is useful in order to monitor response to treatment, to assess presence of co-morbid sleep disorders such as obstructive sleep apnea or periodic limb movement disorder, and to address psychosocial issues that often arise.

No new articles since the prior review were identified in the literature regarding the use of a comprehensive approach for management of hypersomnia due to narcolepsy or the other hypersomnias covered in this paper. However, continued application of the same comprehensive approach as that outlined previously

for narcolepsy appears reasonable for the care of patients with hypersomnia.

## 5.0 ADVERSE SIDE EFFECTS AND SAFETY CONSIDERATIONS

Information about safety and adverse effects of these medications was obtained from a variety of sources, including the articles identified in our literature search regarding treatment efficacy, articles identified in an independent safety search, and from the Physicians' Desk Reference.<sup>31</sup> Because of our search strategy and publication patterns in this area over the past several years, the majority of articles reviewed contain information about adverse effects from studies regarding modafinil and sodium oxybate. Information regarding adverse effects of traditional stimulants is available in previous AASM publications, and limited information is presented based on our review of the Physician's Desk Reference.<sup>21,29-31</sup> We have summarized information from these sources in Table 6 (provided on the AASM website, [www.aasmnet.org](http://www.aasmnet.org)), and Table 7 provided in the text. Although our review is systematic and clinically focused, it is not exhaustive and the reader may need to seek additional sources for certain types of information. The scope of our search involved identification of adverse side effects, pediatric issues, and risks associated with use of these medications in pregnant or breastfeeding women. We identified no information regarding pregnant or breastfeeding women other than that contained in the PDR.<sup>31</sup> The following discussion of safety issues is organized by medication.

### 5.1 Alerting Agents

#### 5.1.1 Modafinil

Twenty-eight articles were identified and reviewed for discussion of safety issues. The majority of adverse events were mild or moderate in severity. Beginning at doses of 100 mg daily, the most commonly reported side effects were headache (10%-26%), nervousness and/or anxiety (3%-20%), nausea (5%-11%), dry mouth (3%-7%), diarrhea (4%-6%), asthenia (4%-6%), and insomnia (3%-6%), all of which occurred at an incidence that was statistically significant as compared to placebo.<sup>63,64,68-70</sup> Only one study indicated a clearly defined dose relationship with respect to severity of adverse effects (involving patients with MS).<sup>64</sup> One study showed no significant differences in the incidence of adverse effects between active treatment and placebo.<sup>38</sup> The adverse effect profile was similar for the controlled and uncontrolled studies that were reviewed.

In general, when investigators reported that subjects withdrew from a study due to adverse effects, withdrawal occurred at a rate ranging from 3%-10%.<sup>64,68-70</sup> Reasons for drug-related discontinuation included dry mouth (33%-50%), headache (29%-50%), heart palpitations (25%-33%), anxiety or agitation (25%), nausea (25%), dizziness (25%), insomnia (25%), depersonalization (25%), and sexual dysfunction (25%).<sup>61,63,64,66,68-70</sup> The open-label study incidence of drug-related discontinuation was identical to that reported above, and reasons for discontinuation were generally similar. However, complaints in open-label studies included more cognitive and psychiatric concerns, such as difficulty concentrating (33%), abnormal thinking (20%-40%), and depression (20%-40%).<sup>36,43,62,65,71</sup>

Several reports describe unique adverse effects in specific patient populations. Although clinically significant changes in vital signs were not described by any of the other studies, a study in-

volving residual sleepiness in patients with obstructive sleep apnea reported hypertension that was felt to be related to modafinil in approximately 4% of the patients, suggesting that this subgroup of hypersomnolent patients may be more susceptible to this effect.<sup>68</sup> In a study of modafinil in patients with MS, 3 of 71 subjects (4%) reported worsening of MS symptoms while receiving the medication. None of the affected individuals required further treatment, and symptoms resolved without adjustment of modafinil dosage.<sup>64</sup> Exacerbation of MS symptoms was also described in 1 patient in an open-label study, necessitating discontinuation of treatment for 5 days.<sup>68</sup>

In 3 placebo-controlled studies that investigated the use of modafinil in Parkinson's disease-associated hypersomnia,<sup>61,63,72</sup> side effects were never reported as severe. In one study,<sup>72</sup> the occurrence of side effects did not differ significantly from placebo. In an open-label study with modafinil, no patients experienced worsening of parkinsonian symptoms but one of 10 subjects experienced visual hallucinations while receiving 100 mg of modafinil. Hallucinations persisted despite discontinuation of the drug, and the patient eventually required treatment with antipsychotic medication.<sup>62</sup> A case report of pramipexole-associated hypersomnia in a Parkinson disease patient described successful treatment with modafinil, with no adverse side effects.<sup>73</sup>

Although one study of modafinil (maximum 200 mg daily)<sup>71</sup> for the treatment of fatigue in association with depression demonstrated a relatively high dropout rate due to adverse events (10%), 2 case series demonstrated no reports of adverse events among adult patients treated with modafinil for hypersomnia in association with depression (bipolar and unipolar).<sup>74,75</sup> High-dose modafinil (800 mg total daily dose) was associated with exacerbation of psychotic symptoms in an adult patient with schizophrenia.<sup>76</sup>

A case report highlighted the importance of medication interactions when modafinil is prescribed with other medications. The author describes a young woman receiving modafinil, methylphenidate, and hypnotics who overdosed and eventually died.<sup>77</sup> However, a separate report described a patient who ingested 4500 mg of modafinil in a suicide attempt followed by full recovery in 24 hours. This observation suggests that overdose of modafinil alone is not likely to have serious consequences.<sup>59</sup> A case report also describes the successful continuation of modafinil with concomitant amphetamine and clomipramine with general anesthesia.<sup>78</sup>

There were limited opportunities to assess adverse effects of modafinil in children. A retrospective study by Ivenenko<sup>41</sup> reported the response of children (mean age 11 yrs [range 2-18]), with narcolepsy and idiopathic hypersomnia with follow-up for a mean duration of 16 months.<sup>41</sup> While modafinil was generally well-tolerated, 2 of 13 (15%) patients experienced exacerbations of preexisting seizures and psychotic symptoms, respectively. The medication was ultimately continued in both instances, with adjunctive anticonvulsants and psychotropic medication. There is one case report of de novo manic symptoms in a 17-year-old boy with narcolepsy treated with modafinil 400 mg daily, ultimately requiring discontinuation of modafinil.<sup>79</sup>

#### 5.1.2 Armodafinil

Two reports were identified in the literature relating to side effects of armodafinil and both of these were placebo-controlled trials. As with modafinil, most adverse effects appear to be mild or moderate in severity.<sup>37,80</sup> With doses of 150 mg or 250 mg daily,

headaches were described in 16%-28% (dose-related), nausea in 7%-14%, dizziness in 2%-8%, insomnia in 7%, and anorexia in 3%-6% of patients. In the study involving patients with OSA,<sup>80</sup> clinically significant increases in specific liver function tests occurred in 1%-3% of subjects. Also reported in this study were statistically significant mean changes (from baseline to final visit) in morning diastolic blood pressure and evening heart rate, but the proportion of patients with clinically significant changes in either parameter were comparable to the placebo group. Subjects withdrew from the study due to adverse effects potentially attributed to medication in 5%-9% of subjects. Reasons for withdrawal (with some subjects reporting 2 reasons simultaneously) included headache (20%-29%), insomnia (14%), diarrhea (14%), disorientation (14%), dizziness (14%), abnormal behavior (14%), and nausea (10%).

### **5.1.3 Methylphenidate, Amphetamines, and Pemoline**

A recent “black box” warning emphasized that amphetamines have a high potential for abuse.<sup>31</sup> The warning indicated that administration for prolonged periods of time may lead to drug dependence and must be avoided. Prescribing physicians should be aware of the possibility of subjects obtaining amphetamines for non-therapeutic use or for distribution to others. The warning also indicated that misuse of amphetamines may cause sudden death and serious cardiovascular adverse events. The AASM issued a statement in August, 2006 that addressed the “black box” warning ([www.aasmnet.org](http://www.aasmnet.org)). The statement reviewed that amphetamine preparations are effective agents for the treatment of sleepiness associated with narcolepsy, and should not be withheld from appropriate patients. They are generally used in patients with more severe sleepiness and when other medications have proven ineffective. The statement also indicated that physicians who prescribe amphetamines should be knowledgeable about the drugs and should carefully assess the risk-benefit ratio for each patient. The statement recommended that a clinical assessment for cardiac disease should be performed, and that patients should be informed about the possibility of adverse side effects.

Pemoline has been associated with potentially fatal hepatotoxicity and is no longer being manufactured or marketed in the United States. During the period from 1975 until June 1999, thirteen cases of acute liver failure in patients receiving pemoline were reported to the FDA.<sup>81</sup> Although this represents a relatively small number of cases, the reported rate ranged from 4 to 17 times the rate expected in the general population.<sup>81</sup>

Review of the literature reveals several recent additions regarding adverse effects associated with traditional stimulants and pemoline. In a study that assessed myotonic dystrophy patients with hypersomnia,<sup>67</sup> 2 of 11 patients (18%) discontinued the medication because of the development of tolerance, and because of intolerable feelings of “personality change.”

Despite concerns among practitioners regarding the risk of hypertension with long-term use of these medications, systematic studies have yet to demonstrate a consistent positive association. Wallin and Mahowald retrospectively studied 54 subjects with narcolepsy or idiopathic hypersomnia who had received uninterrupted stimulant treatment (methylphenidate, pemoline, and dextroamphetamine) for a minimum of 2 years and a mean of nearly 4 years.<sup>82</sup> Methylphenidate, either alone or in combination with pemoline, was used in 80% of patients, and 30% of

subjects were using high-dose stimulants, as defined by the original American Sleep Disorders Association criteria.<sup>30</sup> No statistically significant change in systolic or diastolic blood pressure was observed during the study period in subjects receiving either the low dose or high dose. Preexisting hypertension did not appear to be a significant variable in predicting blood pressure changes.

In contrast, a case report describes a young man who developed a lacunar stroke during methylphenidate use (prescribed 60 mg daily), without a concurrent history of substance misuse or known cardiovascular risk factors.<sup>83</sup> In a case-control study comparing patients receiving high-dose stimulants to those receiving standard dosages (methylphenidate was most commonly prescribed), the odds for developing tachyarrhythmias were approximately 3-fold in the high-dose group.<sup>84</sup>

The most worrisome adverse effects among those receiving high-dose stimulants appear to be psychiatric, as demonstrated by the higher frequency of psychosis, substance misuse, and psychiatric hospitalization compared to those receiving standard doses.<sup>84</sup> The odds ratio for psychosis when comparing the two groups was 12.0. Anorexia or weight loss was also more common in this group.

### **5.1.4 Selegeline Hydrochloride**

One placebo-controlled study using selegeline was identified in patients with narcolepsy.<sup>85</sup> One of thirty patients (3%) discontinued the protocol due to severe headache attributed to the drug. No other side effects were reported.

### **5.1.5 Ritanserin**

One placebo-controlled study was identified that utilized this medication in patients with narcolepsy.<sup>52</sup> Although specific details were not reported, 6% of patients dropped out of the study due to adverse events (constipation, confusion, somnolence, bronchospasm, dry mouth, tongue paralysis). However, the proportion of subjects receiving active drug versus placebo was not reported.

### **5.1.6 Reboxetine**

One open-label pilot study assessed both stimulant and anticholinergic effects of reboxetine in patients with narcolepsy.<sup>50</sup> Specific descriptions of the incidence of side effects were not reported, but all patients successfully completed the protocol. Only minor side effects were reported, including dry mouth, hyperhidrosis, constipation, and restlessness.

## **5.2 Anticholinergics**

### **5.2.1 Sodium Oxybate**

Nine articles were reviewed for safety issues, including 4 placebo-controlled studies. Most reports indicated that adverse effects were of mild or moderate severity, but 4 studies reported serious effects potentially related to the drug.<sup>46,54,86</sup> One study suggested that the incidence of adverse effects may be higher in females, due to a higher mg/kg ratio as compared to males. However, these events were observed primarily in an experimental state of relative starvation. Dosage adjustments based on gender

were not felt to be warranted in the usual setting.<sup>87</sup>

At doses ranging from 3-9 g nightly, adverse effects were dose-related and included dizziness in 12%-34%, nausea in 6%-34%, enuresis in 6%-14%, and vomiting in 6%-11%.<sup>46,54</sup> Among the open-label studies, some of which allowed for assessments of extended treatment duration, the side effect profile was similar to that described above, but also included reports of headaches (23%), anorexia (12%), back pain (12%), and edema (12%).<sup>48,49,88</sup>

One placebo-controlled trial reported in two manuscripts assessed the effects of abrupt discontinuation of drug after long-term therapy.<sup>55,89</sup> The occurrence of adverse events in active and placebo treatment groups was insignificant. No symptoms of frank withdrawal or serious events were reported, and there was no evidence of rebound cataplexy, in contrast to reports involving abrupt antidepressant withdrawal.

When subjects withdrew as a result of adverse effects potentially attributed to drug, this occurred at a rate ranging from 7%-12%.<sup>46,48,49,54</sup> Although the reasons for withdrawal were described as mild or moderate in severity in most cases, the specific incidence of each event was not always explicitly stated. Adverse events included abnormal coordination, amnesia, apathy, asthenia, decreased libido, depression, respiratory complaints, hypesthesia, headache, metallic taste, nervousness, somnolence, stomach upset, weight loss, and psychosis.<sup>46,48,49</sup> The latter event occurred in a patient with preexisting mental illness.<sup>49</sup>

Serious adverse events resulting in withdrawal from study included an acute confusional state in 1 patient,<sup>46</sup> an accidental fall and ankle fracture in a patient with preexisting vertigo, and elevated liver function tests in an additional patient.<sup>54</sup> Elevated liver enzymes were also described in a long-term open-label study, but were not deemed to be of clinical significance.<sup>49</sup> A separate open-label study also described agitation in response to the medication in an elderly woman. The agitation was deemed serious in nature, but the patient was ultimately able to resume participation in the trial.<sup>49</sup>

Reported laboratory abnormalities included a slight increase in urine pH at a 9 g per night dosage, attributed to increased sodium consumption associated with the drug.<sup>46</sup> Changes in serum phosphorus and calcium were noted across dose groups in one study, but these were deemed to be clinically insignificant.<sup>49</sup> The same study reported a mild decrease in diastolic blood pressure across treatment groups, with a maximum change of 7 mm Hg.

One retrospective study afforded the opportunity to assess effects of the medication in a pediatric population (mean age 13.75[9-16]), utilizing doses from 3-7 g nightly, for a mean treatment duration of approximately 11 months.<sup>86</sup> Among the 8 patients studied, 2 (25%) described terminal insomnia, 1 (12.5%) described constipation, 1 (12.5%) described tremors, and 2 subjects (25%) required discontinuation of the medication due to adverse effects. One subject described "dissociated feelings" and the other (with preexisting mental illness) endorsed increased nightmares and suicidal ideation.

### **5.2.2 Antidepressants**

A variety of antidepressants are used in the clinical setting for treatment of cataplexy. However, the literature is sparse with regard to adverse side effects for this indication. A single report described a case of prolonged rebound cataplexy (one episode lasting 25 minutes) after cessation of fluoxetine in preparation for

performing the multiple sleep latency test. Symptoms resolved upon resumption of the medication.<sup>90</sup>

## **6.0 DISCUSSION**

Our review of the literature indicates that the majority of articles that meet inclusion criteria pertain to modafinil or sodium oxybate for treatment of narcolepsy, and that most published studies of modafinil or sodium oxybate were pharmaceutical industry supported. Of the 33 articles reviewed and graded, 25 studies evaluate subjects with narcolepsy or idiopathic hypersomnia, 7 involve subjects with hypersomnia due to a medical condition (3 studies regard Parkinson disease, 2 regard multiple sclerosis, and 2 regard myotonic dystrophy), and 1 involves recurrent hypersomnia. Twenty studies report results of trials with modafinil or armodafinil, and seven report trials involving sodium oxybate. Only one study reports results that involve a traditional stimulant. This was a small open label study that reported the results of methylphenidate treatment of sleepiness associated with myotonic dystrophy.

These findings reflect a clear shift toward investigation and reporting of newer therapeutic agents, and as noted, the majority of newer studies are supported by the pharmaceutical industry. This observation is in contrast to the widespread use of traditional stimulants in the United States, presumably due to continuation of prior usage patterns, the view that traditional stimulants are generally more potent than the newer medications, and possibly cost and insurance coverage issues.

Among studies that involve subjects with narcolepsy or idiopathic hypersomnia, nine were graded as level 1, five were level 2, 1 was level 3, and ten were level 4. In contrast, among studies that involve subjects with other forms of hypersomnia, only one study provided level 1 evidence, 3 studies had level 2 evidence, and 4 had level 4 evidence. Thus, studies of narcolepsy or idiopathic hypersomnia had generally higher evidence levels than studies that involve other forms of hypersomnia of central origin.

Our review identified a number of studies that indicate that modafinil and sodium oxybate are effective and generally well tolerated for treatment of sleepiness associated with narcolepsy. Most studies document optimal therapeutic response with 200 mg to 400 mg per day of modafinil, and several studies provide evidence of more sustained alertness across the day using a split-dose regime. Optimal therapeutic response to sodium oxybate is generally demonstrated with 6 g to 9 g of medication given in two divided doses at night. However, we identified no clinical trials that provide head-to-head comparison of traditional stimulants versus newer agents such as modafinil or sodium oxybate for treatment of narcolepsy. The study by Black et al.<sup>33</sup> allowed for comparison of modafinil and sodium oxybate and the combination of the two in a randomized placebo-controlled trial. This study provides evidence that supports a somewhat better therapeutic response with sodium oxybate compared with modafinil, as assessed by objective (MWT) and subjective (ESS) measures. Two of the large studies using sodium oxybate for treatment of narcolepsy symptoms allowed subjects to continue receiving stimulant medications, indicating possible additive or synergistic effects. The absence of comparative studies leaves unanswered the question of which medications are the most efficacious and best tolerated, and whether certain subgroups of patients may respond better to some medications than others.

Clinical practice patterns suggest that modafinil is currently viewed as the initial drug of choice for treatment of sleepiness associated with narcolepsy<sup>91</sup> (*Task Force, personal observations*). However, there are no data available to indicate what proportion of patients treated initially with modafinil require transition to a traditional stimulant, to sodium oxybate, or to combination therapy. As stated, only one study<sup>33</sup> provides data regarding comparison of modafinil, sodium oxybate, a combination of the two medications, and placebo.

As with the traditional stimulants, modafinil and sodium oxybate provide, at best, only moderate improvement of sleepiness rather than full restoration (normalization) of alertness in patients with narcolepsy. Despite progress in understanding the pathogenesis of narcolepsy, the ideal treatment for sleepiness due to narcolepsy is not yet available.

Our review also revealed no studies that provide a direct head-to-head comparison of antidepressants and sodium oxybate for treatment of cataplexy. As with the treatment of hypersomnia, studies that involve direct comparison of therapeutic agents would provide the best method for evaluating optimal efficacy and tolerability of medications for cataplexy.

Our findings indicate that very few reports provide information regarding treatment of special patient populations with hypersomnia. Only one study that met inclusion criteria involved treatment of children with narcolepsy or idiopathic hypersomnia with modafinil.<sup>41</sup> Older adults were well represented in three studies of patients with Parkinson disease and hypersomnia.<sup>61-63</sup> We identified no studies that provide information regarding pregnant or breastfeeding women.

The available literature provides little information regarding patient preferences among the different medications or patient compliance in “real world” circumstances. Few studies assess whether improvements in subjective or objective measures of sleepiness translate into improvement in quality of life, safety, job performance, or academic performance. Although no specific data are available, it is likely that cost differences and drug availability on formularies also influence clinical decision making regarding use of these medications.

Current approaches to treatment of narcolepsy and other hypersomnias of central origin remain symptomatic in nature. In addition to pharmacological intervention, comprehensive management should emphasize patient education and support, treatment of co-morbid conditions, and long-term follow up to monitor for medication side effects and tolerance.

## 7.0 SUMMARY AND FUTURE DIRECTIONS

The majority of recent articles in the literature report results of studies of modafinil or sodium oxybate for treatment of sleepiness due to narcolepsy. Based on several large randomized, placebo-controlled studies, modafinil and sodium oxybate are effective for treatment of hypersomnia associated with narcolepsy. Several large randomized, placebo-controlled studies demonstrate that sodium oxybate is effective for treatment of cataplexy. We identified no studies with direct comparison of traditional stimulants versus newer medications such as modafinil or sodium oxybate for treatment of sleepiness. Similarly, we identified no studies that report direct comparison of antidepressants or sodium oxybate for treatment of cataplexy. As noted in earlier studies of traditional stimulants, modafinil and sodium oxybate provide, at best, only

moderate improvement in sleepiness rather than complete restoration (normalization) of alertness in patients with narcolepsy.

The literature contains very few studies that involve special populations with hypersomnia such as children, older adults, or pregnant or breastfeeding women. There is little information regarding patient preference, patient compliance, or the impact of cost and drug availability in formularies on decision making regarding medications for treatment of pathological sleepiness or cataplexy.

Current treatment options for narcolepsy and other hypersomnias of central origin remain symptomatic in nature. Despite significant advances in understanding the pathophysiology of narcolepsy, we do not have an ideal treatment to completely restore full and sustained alertness across the day. Future investigations should be directed toward development of more effective and better tolerated therapies, and primary prevention.

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