

# Current and Future Treatment Options for Narcolepsy: A Review

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## ABSTRACT

Narcolepsy is a chronic neurological sleep disorder with potentially disabling symptoms ranging from occupational concerns to mental health difficulties. Recent advances related to the neurobiological basis of narcolepsy have led to newer pharmacological treatment options and adjunctive behavioral techniques that support symptom management. This article outlines evidence-based pharmacologic therapies, behavioral techniques, and psychosocial costs related to narcolepsy. Psychosocial factors, although frequently acknowledged, deserve further attention and awareness from researchers and providers. The American Academy of Sleep Medicine's (AASM) Quality Measure Drivers and potential future treatment options are also discussed.

**Keywords:** Narcolepsy; Therapeutics; Pharmacologic actions; Behavioral medicine; Psychosocial impact.

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## INTRODUCTION

Narcolepsy is a lifelong neurological sleep disorder with potentially disabling symptoms that are developmental in nature<sup>1</sup>. Approximately .05 percent of the U.S. population, and 1 out of 2,000 persons worldwide, are living with narcolepsy<sup>2</sup>. For most individuals, symptoms present in the first two decades of life, typically prior to age 25<sup>3</sup>. There are no differences in rates of narcolepsy among men and women. Prevalence rates are also consistent across countries, yet some studies conducted in Japan have indicated higher rates<sup>3,4</sup>.

The two major forms of narcolepsy, as identified by the American Academy of Sleep Medicine (AASM)—Narcolepsy type 1 (Na-1) and Narcolepsy type 2 (Na-2)—are central disorders of hypersomnolence (CDH)<sup>5,6</sup>. CDH are largely characterized by excessive daytime sleepiness (EDS), which is a hallmark symptom of both Na-1 and Na-2. Na-1 results from a loss of cerebrospinal fluid (CSF) hypocretin-1 concentration and is accompanied by cataplexy, whereas Na-2 does not involve cataplexy or low levels of CSF hypocretin-1<sup>5,6</sup>.

The National Institute of Neurological Disorders and Stroke termed cataplexy as a “sudden loss of muscle tone while the person is awake that leads to feelings of weakness and a loss of voluntary muscle control” (p. 5)<sup>7</sup>. Episodes of cataplexy develop over several seconds and individuals remain entirely conscious—a feature that differentiates them from seizures—regardless of the varying duration and intensity that have been reported. The severity of cataplexy episodes can range from mild weakness of facial muscles (e.g., drooping of eyelid) to a complete loss of tone in voluntary muscles<sup>7</sup>.

Excessive daytime sleepiness, the cardinal feature of narcolepsy, is also typically the first presenting symptom<sup>3</sup>. EDS is regularly accompanied by sleep attacks, which are abrupt involuntary sleep episodes lasting anywhere from a few seconds to several minutes<sup>7</sup>. Sleep paralysis and interrupted nighttime sleep are also very common, whereas hallucinations and automatic behaviors have been reported with less frequency<sup>8</sup>. Sleep paralysis is described as “the disturbing temporary inability to move voluntary muscles at sleep-wake transitions,” usually occurring at the point of waking and less often at the point of falling asleep (p. 270)<sup>3</sup>. A surprising, yet common symptom of narcolepsy is substantial fragmentation in nocturnal sleep, which reduces the quality of sleep thus increasing the severity of daytime symptoms.

The diagnostic criteria for narcolepsy are outlined in the AASM *International Classification of Sleep Disorders – Third Edition (ICSD-3)*<sup>5</sup>. The American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5)*<sup>9</sup> also outlines diagnostic criteria, particularly for clinicians who are not experts in sleep medicine. Specifically, the *DSM-5* specifies a need for a formal sleep study conducted by “a medical professional,” indicating that the appropriate referral must be made for testing prior to diagnosis.

Potential etiological factors for narcolepsy include genetics, CSF hypocretin-1 deficit, and other relevant environmental conditions<sup>4,7,10</sup>. Narcolepsy has been linked

with a set of DNA variations, the HLA DR2 haplotype, and this suggests that the condition may potentially result from an autoimmune process<sup>4,11</sup>. A loss in hypothalamic neurons containing the neuropeptide, hypocretin, is strongly associated with Na-1 (formerly known as narcolepsy with cataplexy)<sup>6,10</sup>. Further, environmental factors, such as flu infections, unexplained fevers, major change in sleeping habits, strokes, tumors, traumatic brain injury (TBI), congenital disorders, and more, have also been found to be related to narcolepsy<sup>4,12</sup>.

The diagnostic methods frequently employed for narcolepsy include comprehensive clinical interview, nocturnal polysomnography (PSG) sleep study, typically followed by a multiple sleep latency test (MSLT), as well as the assessment of CSF hypocretin-1 levels when warranted<sup>7,13,14</sup>. Actigraphy tools and self-report measures (e.g., sleep logs, Epworth Sleepiness Scale, etc.) are frequently used as supplemental diagnostic tools<sup>14</sup>. Additional diagnostic approaches for narcolepsy are limited and many persons with narcolepsy experience a 10- to 15-year diagnostic delay before they finally receive accurate diagnosis and treatment<sup>1,15</sup>, demonstrating the need for more research in this area.

At present, there is no cure for narcolepsy, and currently available treatment methods are not entirely effective in managing all symptoms. Existing pharmacological and behavioral treatment approaches have nonetheless led to significant improvements in the quality of life of many persons living with narcolepsy<sup>10</sup>.

## PHARMACOLOGIC THERAPIES

Pharmacological interventions are the most common approach for treating narcolepsy, and medications are prescribed based on symptom presentation: (1) EDS and sleep attacks; (2) disturbed nighttime sleep, and; (3) cataplexy, hypnagogic hallucinations, and sleep paralysis (see Table 1)<sup>16</sup>. Current medications have been developed to target symptoms, yet most people continue to experience the negative impacts associated with their symptoms despite receiving standard treatment<sup>17</sup>.

### Excessive daytime sleepiness and sleep attacks

EDS is always present in those diagnosed with narcolepsy, and it is the symptom most commonly reported as problematic by patients<sup>17</sup>. Excessive sleepiness is typically the first symptom to present and over 90 percent of patients depend on medications to combat sleepiness each day. Though medications do not lead to complete relief from EDS, they have been effective in preventing hazardous accidents resulting in serious injury or death<sup>7</sup>. For example, people living with untreated EDS and additional related symptoms have approximately ten times as many automobile accidents compared to the general population, whereas persons with narcolepsy receiving appropriate medication for EDS and related symptoms have comparable rates to the general population<sup>7</sup>.

**Table 1.** Overview of Pharmacologic Approaches.

Drug Class	Examples with EMA/FDA approval status (with brand names)	Treatment Indications	Recommended Daily Dosage
Stimulants	<ul style="list-style-type: none"> <li>• Amphetamine salts<sup>FDA</sup> (Adderall)</li> <li>• Dextroamphetamine<sup>FDA</sup> (Dexedrine, Zenzedi)</li> <li>• Methylphenidate<sup>EMA, FDA</sup> (Ritalin)</li> <li>• Dexmethylphenidate (Focalin)</li> <li>• Lisdexamfetamine (Vyvanse)</li> </ul>	<ul style="list-style-type: none"> <li>• excessive daytime sleepiness</li> <li>• sleep attacks</li> </ul>	<ul style="list-style-type: none"> <li>• 5-60 mg of amphetamine salts (sometimes split doses)</li> <li>• 20-40 mg of methylphenidate</li> </ul>
Wakefulness-Promoting Agents	<ul style="list-style-type: none"> <li>• Modafinil<sup>EMA, FDA</sup> (Provigil)</li> <li>• Armodafinil<sup>FDA</sup> (Nuvigil)</li> </ul>	<ul style="list-style-type: none"> <li>• excessive daytime sleepiness</li> <li>• sleep attacks</li> </ul>	• 100-400 mg (sometimes split doses)
Sodium Oxybate	Gamma-hydroxybutyrate <sup>EMA, FDA</sup> approved for EDS and cataplexy (Xyrem <sup>®</sup> )	<ul style="list-style-type: none"> <li>• excessive daytime sleepiness</li> <li>• sleep attacks</li> <li>• cataplexy</li> <li>• sleep paralysis</li> <li>• hypnagogic hallucinations</li> <li>• disturbed nocturnal sleep</li> </ul>	4.5-9 g (split dose at night)
Antidepressants	<ul style="list-style-type: none"> <li>• TCAs (Clomipramine, Imipramine)</li> <li>• SSRIs (Prozac, Celexa)</li> <li>• SNRIs (Effexor, Pristiq)</li> </ul>	<ul style="list-style-type: none"> <li>• cataplexy</li> <li>• sleep paralysis</li> <li>• hypnagogic hallucinations</li> </ul>	Varies
Benzodiazepines Hypnotics	(Triazolam, Ambien)	disturbed nocturnal sleep	Varies

EMA Approved by the European Medicines Agency. FDA Approved by the U.S. Food and Drug Administration.

### Stimulants

Stimulants, such as amphetamines/dextroamphetamines and methylphenidate, are the conventional medications prescribed for symptom management, particularly EDS<sup>18</sup>. These medications promote alertness by increasing monoaminergic activity, specifically targeting the neurotransmitters dopamine and norepinephrine<sup>16</sup>. Stimulants have not been effective in treating most cases of cataplexy, particularly when the symptoms are more severe. Currently, amphetamines/dextroamphetamines and methylphenidate are typically prescribed as ancillary medications for narcolepsy treatment when the first-line forms of pharmacologic therapies (e.g., modafinil/armodafinil and sodium oxybate) are not fully effective in treating EDS, or patients are unable to take these medications<sup>16,18</sup>.

Stimulants can be highly addictive<sup>4</sup> and higher doses have been associated with more frequent hospitalizations, cardiac arrhythmias, and psychiatric disturbances<sup>16</sup>. Furthermore, it is noteworthy that stimulant usage may play a significant role in the diagnostic delay of narcolepsy, which is found across countries<sup>16</sup>. Specifically, stimulants are primarily used to treat attention deficit hyperactivity disorder (ADHD), which is characterized by a number of symptoms similar to those found in narcolepsy, including drowsiness, decreased alertness and attention, and additional cognitive difficulties<sup>19</sup>. Importantly, the frequent comorbidity of ADHD and narcolepsy raises the concern for potential misdiagnosis among individuals with symptoms of narcolepsy, ADHD, or both<sup>19</sup>. For example, when stimulants are prescribed for attention problems, it can lead to the masking of narcolepsy symptoms such as excessive daytime sleepiness.

### Wakefulness-promoting agents

Modafinil and armodafinil are wakefulness-promoting agents that are FDA (U.S. Food and Drug Administration) approved for the treatment of EDS in narcolepsy and other sleep disorders<sup>4,16</sup>. Though their mechanism of action is not entirely understood, the wakefulness-promoting agents are known to work in the dopaminergic, adrenergic, and histaminergic systems of the hypothalamus<sup>4,10,16</sup>. In recent years, modafinil and armodafinil started replacing the traditional option of stimulants in treating excessive sleepiness due to the side effects and potential for addiction of stimulants<sup>16</sup>. However, these wakefulness-promoting agents remain the conservative approach in treating EDS compared to sodium oxybate, which has been identified as a more effective treatment option due to better responses from patients and fewer weekly sleep attacks<sup>18</sup>.

### Sodium oxybate

Sodium oxybate, also known as gamma-hydroxybutyric acid (GHB), is a more recent medication effective in treating narcolepsy. It is the only medication proven effective, and is recommended by the FDA, for treating both EDS and cataplexy<sup>4</sup>. It improves EDS symptoms by increasing the quality of nocturnal sleep, which then leads to an improvement in narcolepsy symptoms during the daytime<sup>16</sup>. It has also been associated with fewer sleep attacks<sup>18</sup>. Its mechanism of action involves the inhibition of the release of different neurotransmitters, including GABA, glutamate, and dopamine<sup>10</sup>. In contrast to stimulants and wakefulness-promoting agents, sodium oxybate was initially developed to be used as a general

anesthetic and is effective in increasing slow-wave sleep<sup>10,16</sup>. It is worthwhile to note that in some studies comparing sodium oxybate to modafinil, both objective and subjective measures revealed sodium oxybate was more effective in treating EDS<sup>4</sup>. Nevertheless, similar to stimulants, GHB can be highly addictive and has been associated with significant abuse, dependence, and withdrawal due to its euphoric effects<sup>4</sup>.

### Disturbed nighttime sleep (DNS)

Although it remains considerably underrecognized, significant fragmentation of nocturnal sleep is a characteristic frequently observed in persons with narcolepsy<sup>20</sup>. Research on the effects and treatment of DNS is scant, and its treatment is largely overlooked across clinical settings<sup>20</sup>. Further, though drugs that demonstrate promising treatment effects have been identified, there is an absence of medications that have been approved by the FDA specifically targeting DNS.

#### *Sodium oxybate*

Sodium oxybate has also been identified as the best available medication for improving quality of nighttime sleep<sup>18</sup>. Although it has not been approved by the FDA for this exact purpose, it is often prescribed for its clinical value, typically in two nightly doses. Specifically, sodium oxybate is linked with increased non-REM 3 (also known as delta or slow-wave) sleep, reduced nocturnal arousals, and enhanced consolidation of REM sleep periods<sup>10</sup>.

#### *Benzodiazepines and hypnotic non-benzodiazepines*

As the conventional approach to treating DNS, there is inadequate research on the complete impact of benzodiazepines and hypnotics on overall quality of nocturnal sleep among persons diagnosed with narcolepsy. While this class of drugs can delay the onset of nighttime arousals during sleep, sodium oxybate has demonstrated greater value in improving continuous nocturnal sleep<sup>18</sup>.

### Cataplexy, hypnagogic hallucinations, and sleep paralysis

Medication options vary between patients diagnosed with Na-1 or Na-2, as most drugs used for treating EDS are not effective in treating cataplexy, hallucinations, or paralysis<sup>21</sup>.

#### *Sodium oxybate*

Despite the absence of FDA-approval, sodium oxybate is clinically effective in managing hypnagogic hallucinations and sleep paralysis, which also helps to improve nighttime sleep<sup>20-22</sup>. Significantly fewer cataplexy episodes were also reported by persons taking GHB, particularly after continued use for approximately two months<sup>18</sup>. Although its mechanism of action is not entirely understood, GHB is recognized as a partial agonist at GABA-B receptors and other neurotransmitter receptors linked to sleep initiation, and the following boost in quality of nighttime sleep is related to a noteworthy reduction in daytime cataplexy symptoms<sup>23,24</sup>.

#### *Antidepressants—SSRIs, SNRIs, and TCAs*

TCAs are the traditional group of medications used for treating cataplexy, although their specific mechanism of action are not fully understood<sup>4</sup>. Recently, serotonin selective reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have tended to replace TCAs in treating cataplexy, sleep paralysis, and hypnagogic hallucinations<sup>18,22</sup>. Antidepressants are not approved by the FDA for narcolepsy treatment, and further rigorous testing is needed to determine their efficacy in treating cataplexy. Nonetheless, providers commonly prescribe antidepressants due to their clinical effectiveness. More specifically, antidepressants that inhibit norepinephrine reuptake (SNRIs), such as venlafaxine, have also been reported as especially effective in treating cataplexy<sup>16,22</sup>.

Worthwhile to mention is that depression, specifically major depressive disorder (MDD), is the most common mood disorder found among persons with narcolepsy<sup>25</sup>. Ohayon found that compared to the general population, three times as many individuals with narcolepsy were taking antidepressant medications<sup>26</sup>. Depression among persons with narcolepsy was not found to be related to the severity of sleepiness, but rather due to feeling they were not in control of their life, particularly soon after being diagnosed<sup>27</sup>. Due to the similarity in symptoms, narcolepsy is commonly misdiagnosed as depression, and vice versa<sup>25</sup>. Such findings also help explain the continued prescription of antidepressants for persons with narcolepsy to treat cataplexy and mood symptoms in the absence of FDA approval and insufficient research documenting their efficacy<sup>18</sup>.

Table 1 lists the major drug classes and examples (with brand names) of common pharmacologic therapies used to treat narcolepsy symptoms, as well as their recommended usage and approval by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA).

## BEHAVIORAL TECHNIQUES

In conjunction with pharmacologic treatments, various behavioral techniques are also frequently recommended by providers for narcolepsy symptom management.

### Patient Education

Narcolepsy is considerably underdiagnosed and underrecognized and many patients rely solely on their providers for information and recommendations. Accordingly, providing relevant education is essential, especially when patients are first diagnosed with narcolepsy, for effective symptom management and treatment<sup>10</sup>. Particularly important is delivering education related to the following: (1) narcolepsy symptoms, (2) the developmental and varying nature of symptom presentation, (3) the impact of symptoms on relationships, work, etc., (4) available pharmacologic and behavioral therapies (e.g., good sleep hygiene), and (5) other lifestyle factors that may affect symptom severity and/or treatment outcomes (e.g., the influence of alcohol on EDS). If appropriate, providers may find it beneficial to involve patients' family members in the

education process. Important to note is that family members are also significantly affected due to the numerous psychosocial implications narcolepsy can bring. Further, the help of family members can not only help patients manage their symptoms, but can also decrease potential safety concerns (e.g., EDS while driving or in hazardous environments).

### Sleep Hygiene

Given that patients with narcolepsy experience poor quality of sleep and significant sleep fragmentation<sup>20</sup>, establishing good sleep hygiene is a powerful technique that is key in successfully managing symptoms<sup>4</sup>. Sleep hygiene involves reoccurring habits and behaviors that contribute to a high quality of sleep. Sodium oxybate, the only medication effective in treating most narcolepsy symptoms, works by improving the quality of nocturnal sleep<sup>16,20</sup>, indicating that higher sleep quality is vital for improving narcolepsy symptoms.

Optimal sleep hygiene for persons with narcolepsy can include sufficient hours of nighttime sleep, consistent sleep-wake habits and patterns, and scheduled brief daytime naps<sup>28-30</sup>. In addition, alcohol, caffeine, tobacco, and heavy meals should be avoided several hours before bedtime<sup>7,30</sup>. An environment that is conducive to sleep (e.g., free of loud noise or harsh light) can also make a significant impact on sleep quality. Body temperature manipulation has also been linked with changes in sleep quality for persons with narcolepsy—a combination of warming of the skin in proximal regions (e.g., thigh, stomach, and forehead) and cooling in distal regions (e.g., fingers and toes) has been associated with improved nighttime sleep and reduced nocturnal wakefulness<sup>31</sup>. This finding implies that, if possible, carefully selecting or adjusting the temperature of the sleeping environment, drinks/foods, and clothing type can help improve sleep quality.

Good sleep hygiene practices can sometimes be difficult to maintain, as many people overestimate how much they sleep and the quality of their sleep<sup>14</sup>. Monitoring sleep practices can help patients maintain good sleep hygiene, and can also provide clinicians with data necessary to evaluate treatment effects, deliver recommendations, and more. Sleep actigraphs, which measure sleep patterns and circadian rhythms<sup>32</sup>, can aid patients in independently managing their symptoms, and can provide clinicians with valuable data. Actigraphs are typically worn on the wrist for weeks at a time and are more objective than self-report assessments<sup>14</sup>.

Baumann et al. strongly advised that two weeks of actigraphy data should be considered conjunctive to the PSG and MSLT results when assessing for narcolepsy symptoms, as patients typically overestimate how much they sleep and can forget to complete the self-report measures<sup>14</sup>. Just as they are valuable ancillary diagnostic tools, actigraphs can greatly improve the quality of treatment a patient receives due to the increased accuracy in data<sup>14</sup> that his or her provider has access to (e.g., sleep changes associated with pharmacologic therapies<sup>32</sup>) when determining the most suitable treatment option(s).

### Strategic Napping

Naps ranging from 15 to 20 minutes scheduled about two to three times per day are particularly effective in treating EDS and improving alertness<sup>3,21</sup>. Naps should not, however, extend beyond 30 minutes because longer naps may be unrefreshing and result in increased drowsiness<sup>14,21</sup>. Planned naps, however, are impractical for many due to the contemporary demands people have at work or at home. As a result, an overwhelming number of individuals with narcolepsy, and their families, encounter significant socioeconomic burdens involving work-related issues, such as higher rates of missed work-days, lower employment rates, and lower income from employment<sup>2,8</sup>.

### Self-Report Assessments

Self-report assessments are widely-used as supplementary tools for the diagnosis and treatment of narcolepsy<sup>1,14</sup>. Though actigraphs deliver more objective data, self-report assessments nevertheless provide patient data related to many different aspects of sleep, including sleep hygiene, intensity of perceived sleepiness, treatment effects, and different facets of cognitive functioning<sup>3</sup>. The Epworth Sleepiness Scale, Maintenance of Wakefulness Test, and Stanford Sleepiness Scale are some examples of self-report assessments that have been validated to measure EDS<sup>21</sup>. Vigilance tests and other neuropsychological assessments are also used to assess attention and related cognitive functioning, as individuals with narcolepsy exhibit greater impairment in certain cognitive domains when compared to those without the disorder<sup>3</sup>.

A sleep log, also referred to as a sleep diary, is another beneficial tool when treating and diagnosing narcolepsy<sup>28</sup>. A sleep log contains information related to patients' sleep habits, such as their bedtime, number of minutes/hours until falling asleep, morning wake time, as well as the number of and duration of nocturnal wakings. Family members can also complete logs based on their observations of the patients' sleep practices, and the two logs (the patients' and family members') are often compared with each other. This type of information is helpful for clinicians in discovering patients' sleep-wake cycles, night-wakings, level of sleepiness and restfulness, treatment effects, and more—most of which are imperative for accurate diagnosis and effective treatment<sup>32</sup>. Baumann et al. instructed that if actigraphs are unavailable, sleep logs must be the minimum method used to gather data on patients' sleep behaviors two weeks prior to a formal sleep study<sup>14</sup>.

### Manipulation of Skin and Body Temperature

Fronczek et al. examined the effect of skin and body temperature variations on wakefulness in individuals with narcolepsy, as they previously determined these patients have warmer skin temperatures in distal regions—fingers, toes, etc.—compared to proximal regions—thighs, stomach, etc.<sup>31,33</sup>. Higher body temperature was found to improve vigilance, implicating that people with narcolepsy can become more or less alert based on, for example, the temperature of the foods or drinks they consume. Further, lower distal skin temperature-cooler hands

and feet—improved participants' wakefulness, whereas warmer temperatures in these areas hastened sleep onset<sup>33</sup>.

These findings suggest that patients can engage in minor lifestyle changes that can maintain and improve wakefulness and alertness, such as wearing clothing with thermoregulation properties, consuming warm meals/drinks, and using fans to keep hands and feet cool. Auxiliary methods of symptom management such as these are important to communicate with patients, especially when pharmacologic approaches are not completely effective.

### Cognitive Behavioral Therapy – Narcolepsy

Although the neurological origin of narcolepsy warrants pharmacological treatment as the primary approach, adjunctive psychotherapy has also demonstrated beneficial effects on successful management of symptoms<sup>34,35</sup>. Specifically, cognitive behavioral therapy for narcolepsy (CBT-N) has increasingly been identified as an important supplement for treatment, and many features of narcolepsy (e.g., depression and hypersomnia) are already regularly treated with cognitive behavioral strategies. CBT-N focuses on managing behaviors of patients with narcolepsy, such as adhering to medication regimens and engaging in good nocturnal sleep hygiene practices<sup>35</sup>.

Based on their review of the literature, Marín Agudelo et al. summarized the following as effective cognitive behavioral techniques for the management of narcolepsy symptoms: (1a) sleep satiation and (1b) scheduled naps to reduce daytime sleep attacks; (2a) systematic desensitization and (2b) stimulus control to lessen cataplexy episodes; (3) imagery rehearsal therapy to reduce the frequency of and cope with hypnagogic hallucinations; (4) hypnosis to decrease the severity of sleep paralysis; (5) cognitive therapy to reduce adverse effects stemming from dysfunctional cognitions; (6) muscle relaxation to manage anxiety that can worsen narcolepsy symptoms; and (7) diet schedule that optimizes alertness and functioning throughout the day and the quality of nighttime sleep<sup>35</sup>.

### Psychosocial Implications

In addition to considering medications and behavioral approaches to treat narcolepsy symptoms, clinicians should also assess patients' psychosocial functioning and overall quality of life<sup>3</sup>. One of the major features of the condition that remains misheard is the profound psychosocial burden it has on affected persons and their families<sup>1,8,17,36,37</sup>. For example, these individuals encounter markedly increased adverse psychosocial costs compared to the general population, including, but not limited to, higher rates of depression and other medical/psychiatric comorbidities, increased rates of concurrent medication usage, lower levels of employment, decreased work productivity, lower income levels, reduced rates of marriage/cohabitation, and more<sup>2,8,38,39</sup>.

An evaluation of psychosocial impacts must be comprehensive in nature to determine worthy avenues of treatment, as psychosocial consequences can range anywhere from interpersonal troubles<sup>8</sup> to financial stressors<sup>1,2,39</sup>. For

instance, patients with narcolepsy who are experiencing difficulties at work due to excessive sleepiness should be informed about their legal rights such as those guaranteed by the Americans with Disabilities Act (e.g., scheduling most arduous tasks during the time of day when they typically are most alert, or modifying work hours to accommodate brief scheduled naps)<sup>7</sup>. Further, support groups can be a powerful resource for patients because they are often likely to become socially isolated due to embarrassment about their symptoms, and/or the misunderstanding or lack of awareness about narcolepsy and its associated consequences among members of their community.

Table 2 presents each of the non-pharmacologic methods used to treat narcolepsy, accompanied by examples.

### AASM'S NARCOLEPSY QUALITY MEASURES DRIVERS

The AASM Narcolepsy Quality Measures Workgroup was charged with developing quality measures in order to enhance the care of patients with narcolepsy<sup>21</sup>. Three outcome measures that are crucial for successful treatment were identified, along with seven process measures. The first outcome measure involves the decrease of EDS levels via the following processes: (1) assessment of sleepiness, and (2) treatment initiation one month following initial diagnosis. The second outcome measure calls for the improvement of diagnostic accuracy by employing processes such as: (3) comprehensive interview of sleep history, and (4) objective sleep assessment, such as PSG and MSLT. The third outcome measure entails the reduction of adverse events by way of three processes: (5) treatment follow-up on a minimum of an annual basis after treatment initiation; (6) documented medication counseling (e.g., side effects and potential interactions with other medications) prior to or during the time of initial prescription, and; (7) documented age-appropriate safety measure counseling (see Krahn et al. for complete details)<sup>21</sup>. In order to deliver best practices to their patients, clinicians should consider pharmacological and behavioral approaches within the context of these established evidence-based quality drivers.

### FUTURE DIRECTIONS

Recent advances in the understanding of the neurobiological basis of narcolepsy have led to the investigation of narcolepsy treatment options extending beyond symptom management<sup>18</sup>. The different areas from which future treatments may emerge consist of further development of pharmacologic therapies<sup>18,23</sup>, immunotherapy<sup>11</sup>, hypocretin-based therapies<sup>17</sup>, endocrine therapy<sup>18</sup>, and skin temperature manipulation<sup>18,31,33</sup>. The current state of research aimed at developing novel narcolepsy treatments largely involves the use of animal models and the findings are showing promise for treatments effective in treating human symptoms<sup>7</sup>.

**Table 2.** Overview of Behavioral Approaches.

Technique	Examples
Education	Narcolepsy symptom characteristics; varying nature of symptom presentation; psychosocial impacts (e.g., at work, in relationships); nocturnal sleep fragmentation; the importance of treatment adherence, such as maintaining good sleep hygiene; lifestyle reorganization; behavioral techniques; pharmacological options and associated side effects; other lifestyle factors that may affect symptom severity and/or treatment outcomes
Sleep Hygiene	Regular sleep-wake pattern; reduction or absence of alcohol consumption; comfortable sleeping environment and body/skin temperature; avoidance of alcohol, tobacco, caffeine, and large meals several hours before bedtime
Strategic Napping	15-20 minute naps scheduled 2-3 times per day
Reoccurring Assessments	Can be objective, subjective, or self-report; evaluate functioning and treatment effects regularly; use sleep actigraphs and/or sleep logs; administer Epworth Sleepiness Scale, Maintenance of Wakefulness Test, Standard Sleepiness Scale, or other related validated measure(s)
Manipulation of Body/Skin Temperature	Maintaining higher body temperature and cooler distal skin temperature for increased alertness; consuming warm foods/drinks during the day; using a fan to keep hands and feet cool
CBT-N	Techniques targeting the behavioral management of narcolepsy symptoms: talk therapy targeting distorted cognitions, treatment adherence, taking medications at appropriate times, maintaining good sleep hygiene, taking scheduled naps, imagery, and hypnosis
Psychosocial Implications	Occupational considerations and professional advocacy (e.g., legal rights); available resources in the community, such as a Narcolepsy Support Group
Additional Practices for Providers (AASM Quality Measures)	Begin treatment one month following initial narcolepsy diagnosis; follow-ups occurring yearly (as a minimum) after initial treatment; documented medication counseling; documented age-appropriate safety measure counseling; continual assessment of sleepiness levels and quality of life

Development of pharmacologic therapies for narcolepsy, such as medications targeting histamine, are under investigation based on the neuropathology underlying the disease<sup>23</sup>. CSF histamine levels are known to be lower among patients with narcolepsy, especially among those who have deficient hypocretin-1 levels<sup>23</sup>. However, histaminergic neurons remain active during cataplexy, thus, histamine is a current target of investigation for its therapeutic effect mostly on EDS. Pitolisant, a histamine receptor inverse agonist, was found to increase wakefulness levels similar to the levels produced by modanifil<sup>23</sup>. Sodium oxybate (GHB), a current treatment for narcolepsy, has a mechanism of action that is a partial agonist at the GABA<sub>B</sub> receptor as the site for GHB-induced inhibition of neurons<sup>40</sup>. Using mouse models, researchers discovered the GABA<sub>B</sub> agonist, R-baclofen, to be more effective than GHB in consolidating sleep and wake hours and decreasing cataplexy<sup>40</sup>.

Based on a genome-wide association study identifying a new narcolepsy-related single nucleotide polymorphism<sup>41</sup>, located next to the carnitine palmitoyltransferase 1B (*CPT1B*) gene expressing the enzyme acylcarnitine, researchers identified oral L-carnitine as a potential therapy for narcolepsy<sup>42</sup>. Among persons with narcolepsy, oral administration of L-carnitine was effective in reducing EDS but did not have therapeutic effects on other narcolepsy features<sup>43</sup>. More recently, trace amine-associated receptor 1 (TAAR1) agonists were identified as providing therapeutic benefit of reducing cataplexy potentially due to the suppression of REM sleep<sup>44</sup>. For treatment approaches leading to increased wakefulness and decreased EDS, the noradrenergic and dopaminergic systems have been the focus of many investigations due to their involvement with sleep/wake functions<sup>7</sup>.

Based on the understanding of narcolepsy as an autoimmune condition, immunotherapy is another potential

treatment under investigation<sup>45</sup>. The disease is hypothesized to develop from an autoimmune attack on hypocretin neurons, and persons at greater risk include those who are genetically susceptible or have encountered environmental factors related to increased susceptibility<sup>6,45</sup>. Narcolepsy has been linked with a set of DNA variations, the HLA DR2 haplotype<sup>11</sup>. The human leukocyte antigen (HLA) DQB1\*06:02 has been found among the majority of persons with typical cataplexy, yet it is also found among some who do not experience cataplexy or control subjects without EDS<sup>6</sup>. Further, although the role of the environment and its interaction with genes is not clearly known, infections in the upper airway nonetheless have been linked with increased onset of narcolepsy across different countries<sup>45</sup>.

It has been well-established that degeneration of the neurons producing HCRT (hypocretin/orexin) in the posterior hypothalamus results in narcolepsy<sup>23</sup>. Hence, hypocretin-based therapies, including administration of hypocretin-1, hypocretin peptide agonists, cell transplantation, and gene therapy, are also under consideration<sup>23,46</sup>. Hypocretin replacement therapy is a promising approach that could be achieved by delivering hypocretin itself or its agonists<sup>46</sup>. However, due to the blood-brain barrier's impermeability to hypocretin-1, only very high doses of hypocretin administered peripherally have produced some therapeutic effects<sup>23,46</sup>. Intranasal administration of hypocretin-1 to the central nervous system was found to have little effect<sup>23</sup>. At present, additional methods aimed at penetrating the blood-brain barrier or finding alternate routes to the CNS are currently underway—see Black et al. for a full review<sup>23</sup>.

Other potential treatment avenues for hypocretin supplementation include viral vector-based delivery of the prepro-hypocretin gene and generation of hypocretin neurons from human pluripotent stem cells<sup>47</sup>. However, such approaches may come with serious side effects and there remains much to

be learned regarding genetic and stem-cell therapies<sup>47</sup>. Overall, hypocretin is undoubtedly an important target for future treatment, but because the reason for hypocretin degeneration remains unclear, it has been especially difficult to examine potential treatment avenues<sup>23</sup>.

Endocrine therapy is another likely option for narcolepsy treatment due to the therapeutic potential that thyrotropin-releasing hormone (TRH) has on the central nervous system<sup>47,48</sup>. TRH and TRH direct or indirect agonists are known to promote wakefulness<sup>18,47</sup> and also to substantially reduce cataplexy in canine narcolepsy<sup>48</sup>. Nonetheless, its therapeutic and adverse effects on human narcolepsy have yet to be discovered.

The literature is very limited regarding the manipulation of skin and body temperature as a method for managing narcolepsy, but Fronczek et al. [as previously mentioned] have provided the community with the groundwork necessary for additional research<sup>31,33</sup>. This is an important area to pursue considering the preliminary findings demonstrated similar benefits for this method as those associated with pharmacological options<sup>23</sup>.

## CONCLUSIONS

The management of narcolepsy symptoms remains a profound challenge for patients, their families, and providers<sup>36</sup>. Currently, there is no cure for the condition and many patients report that medications are not improving their complete range of symptoms<sup>16</sup>. Narcolepsy is greatly underdiagnosed and underrecognized, yet comes with substantial psychosocial costs<sup>1</sup>. Importantly, the magnitude of burden associated with the illness has been described as “striking” (p. 529) and many underscore the need for additional studies on narcolepsy<sup>2</sup>. These efforts can help advance diagnostic tools contributing to a reduction in the substantial diagnostic delay and discoveries of more effective treatment approaches. Increased awareness and recognition of narcolepsy, its symptoms, and associated psychosocial consequences, is lacking among the general population and notably, among health care providers<sup>15,37</sup>. Educational opportunities particularly on the associated psychosocial repercussions will be vital for raising awareness and reducing the many burdensome costs that fall on persons with narcolepsy<sup>1,2,25,37</sup>.

## CONFLICT OF INTEREST

The authors have no conflicts of interest in this article.

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