

## REVIEW ARTICLE

# The Medical and Economic Burden of Narcolepsy: Implications for Managed Care

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**BACKGROUND:** The neurologic disorder narcolepsy results from dysregulation of the sleep-wake cycle and is primarily characterized by chronic, severely excessive daytime sleepiness and cataplexy, an emotionally induced muscle weakness. The prevalence of narcolepsy is approximately 0.05%, and onset generally occurs during the first 2 decades of life. Narcolepsy is believed to be an autoimmune disorder with destruction of hypocretin-producing neurons in the lateral hypothalamus.

**OBJECTIVES:** To provide an enhanced understanding of narcolepsy and establish the need for early diagnosis and rapid initiation of effective treatment for patients with narcolepsy.

**DISCUSSION:** Narcolepsy reduces daily functioning and is associated with a substantial medical and economic burden, with many patients being on full disability. The annual direct medical costs are approximately 2-fold higher in patients with narcolepsy than in matched controls without this condition (\$11,702 vs \$5261, respectively;  $P < .0001$ ). Further contributing to the overall burden is a lack of recognition of the signs and symptoms of narcolepsy and an absence of easily measurable biomarkers, resulting in a diagnostic delay that often exceeds 10 years and may be associated with misdiagnosis and inappropriate resource utilization. Because narcolepsy generally has an onset in childhood or in adolescence, is often misdiagnosed, has no known cure, and requires lifelong treatment, it is an important disease from a managed care perspective. Clinical features, as well as objective testing, should be used to ensure the timely diagnosis and treatment of patients with narcolepsy.

**CONCLUSION:** Policies for the diagnosis and treatment of narcolepsy should be based on the current treatment guidelines, but they should also encourage shared decisions between clinicians and patients to allow for individualized diagnostic and treatment choices, as suggested in best practice recommendations.

**KEY WORDS:** cataplexy, chronic sleepiness, cost containment, daytime sleepiness, managed care, narcolepsy, prevalence, rapid eye movement sleep

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Narcolepsy is a chronic neurologic disorder, and because there is no known cure, there is a need for lifelong treatment. Narcolepsy results from dysregulation of the sleep-wake cycle and is clinically characterized by a pentad of main symptoms that include excessive daytime sleepiness, cataplexy, hypnagogic or hypnopompic hallucinations (ie, hallucinations during the periods from wakefulness to sleep or from sleep to wakefulness, respectively), sleep paralysis, and disrupted nighttime sleep.<sup>1</sup>

The clinical hallmark of narcolepsy is excessive daytime sleepiness, which is present in all patients and is generally the first symptom to occur.<sup>2,3</sup> In contrast, cata-

plexy, which is considered pathognomonic for narcolepsy and is often triggered by emotions, including fear, anger, or laughter, is present in at least 50% of adults and children with narcolepsy.<sup>2,4</sup> The other symptoms of narcolepsy have a variable prevalence and may not necessarily occur in everyone with the disease.<sup>2,3</sup>

Our current understanding of the etiopathogenesis of narcolepsy, especially in those with narcolepsy associated with cataplexy (ie, narcolepsy type 1), is that the majority of patients have destruction of neurons that produce hypocretin-1 (orexin A), resulting in a reduction of cerebrospinal fluid (CSF) hypocretin levels.<sup>5</sup> Hypocretin is a neurotransmitter that has been shown in animal models to maintain wakefulness, increase arousal, and suppress rapid eye movement (REM) and non-REM sleep.<sup>6</sup> The hypothesis that narcolepsy is likely an immune-mediated disease with autoimmune components is supported by several observations, in-

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## KEY POINTS

- Narcolepsy affects the patient's daily functioning and is associated with a substantial medical and economic burden.
- The diagnosis of narcolepsy is often delayed by up to 12 years, because its signs and symptoms are often confused with other conditions and because of the absence of easily measurable biomarkers.
- Misdiagnosis and inappropriate resource utilization further add to the challenge of early treatment, resulting in increased total costs associated with narcolepsy.
- The annual direct medical costs are approximately twice as high in patients with narcolepsy as in controls without this condition (\$11,702 vs \$5261).
- Narcolepsy has no known cure and requires lifelong treatment, which further increases the economic burden.

cluding the identification of specific genotypes, such as the human leukocyte antigen (HLA)-DQB1\*0602 and T-cell receptor polymorphisms, which have been implicated in regulatory pathways that may contribute to the destruction of hypocretin-producing neurons.<sup>7,8</sup> Narcolepsy has also been found to be associated with specific infections (ie, streptococcus and H1N1 influenza) and H1N1 vaccination.<sup>9</sup>

Although the prevalence of narcolepsy is low, between 0.02% and 0.06% in industrialized countries,<sup>10</sup> the associated healthcare costs are disproportionately high, with direct medical and pharmacy costs that are twice that of the general population.<sup>11</sup> The prevalence of narcolepsy in the US pediatric population is estimated at 20 to 50 per 100,000 children<sup>12</sup>; however, the costs associated with younger patients have not been well-studied. The median age of onset is 16 years,<sup>10</sup> which results in the need for a long duration of treatment.

Despite its low prevalence, narcolepsy is associated with impaired function on a daily basis and has a recognized socioeconomic burden, including increased medical costs relative to the general population,<sup>11</sup> an increased risk for work-related or vehicular accidents,<sup>13,14</sup> and reduced quality of life.<sup>15</sup> In addition, work-related productivity is affected. Although data on the indirect costs of narcolepsy are limited, relative to matched controls of the general population, patients with the disease report significantly higher costs related to work absenteeism (\$7631 vs \$12,839, respectively;  $P < .001$ ) and presenteeism (\$4987 vs \$7013;  $P < .001$ ).<sup>16</sup> The annual

short-term disability costs per employee were also estimated to be 200% higher among employees with narcolepsy relative to the matched controls (\$876 vs \$292, respectively;  $P < .0001$ ),<sup>11</sup> and many patients may be on long-term disability.<sup>16,17</sup>

Recent results from a large claims database study highlight the magnitude of the difference in resource utilization and costs between patients with narcolepsy and matched controls.<sup>11</sup> As seen in the **Figure**, for all the resource categories evaluated (ie, emergency department use, hospitalizations, outpatient visits, and medications), the costs were significantly higher in the narcolepsy cohort, by approximately 2-fold, than in the control group (\$11,702 vs \$5261, respectively;  $P < .0001$ ).<sup>11</sup>

Adults with narcolepsy have a greater prevalence of medical and psychiatric comorbidities compared with the controls without narcolepsy.<sup>16,18,19</sup> In particular, a higher proportion of patients with a Charlson Comorbidity Index score  $\geq 3$  was seen among patients with narcolepsy relative to the controls without narcolepsy (21.7% vs 4.0%, respectively), and patients with narcolepsy were almost twice as likely to report depression (48.3% vs 25.9%, respectively;  $P < .001$ ) and anxiety disorder (40.7% vs 17.7%, respectively;  $P < .001$ ), and almost 3 times as likely to have bipolar disorder (14.2% vs 4.6%, respectively;  $P < .001$ ).<sup>16</sup> Furthermore, an analysis of longitudinal claims for 173 million patients with narcolepsy reported that narcolepsy is associated with a significant 1.5-fold excess mortality rate ( $P < .001$ ) relative to a population without narcolepsy.<sup>20</sup>

In addition, specific issues are associated with pediatric narcolepsy that may affect outcomes and costs and may add to the complexity of patient management. In particular, psychosocial development may be delayed, including decreased academic performance and greater behavioral, personality, and social difficulties.<sup>21-25</sup> High levels of depressive symptoms have also been reported in children with narcolepsy.<sup>26</sup> Furthermore, obesity and precocious puberty are reported to be more prevalent in children with narcolepsy than in those without narcolepsy.<sup>27</sup>

Although the underlying cause of this relationship has not been fully elucidated, these factors, especially obesity, may exacerbate the burden of narcolepsy by also affecting sleep, fatigue, and academic performance.<sup>28</sup> Clinical observation identifies that the presence of obesity, when associated with episodes of obstructive sleep apnea, frequently leads to a diagnosis of obstructive sleep apnea syndrome without recognition of the concurrent symptoms of narcolepsy, leading to further delay in the diagnosis and treatment of narcolepsy.

The purpose of this article is to increase the understanding of narcolepsy and the clinical needs that may be

considered when establishing managed care policies regarding its diagnosis and management.

**Narcolepsy Management Challenges in Diagnosis**

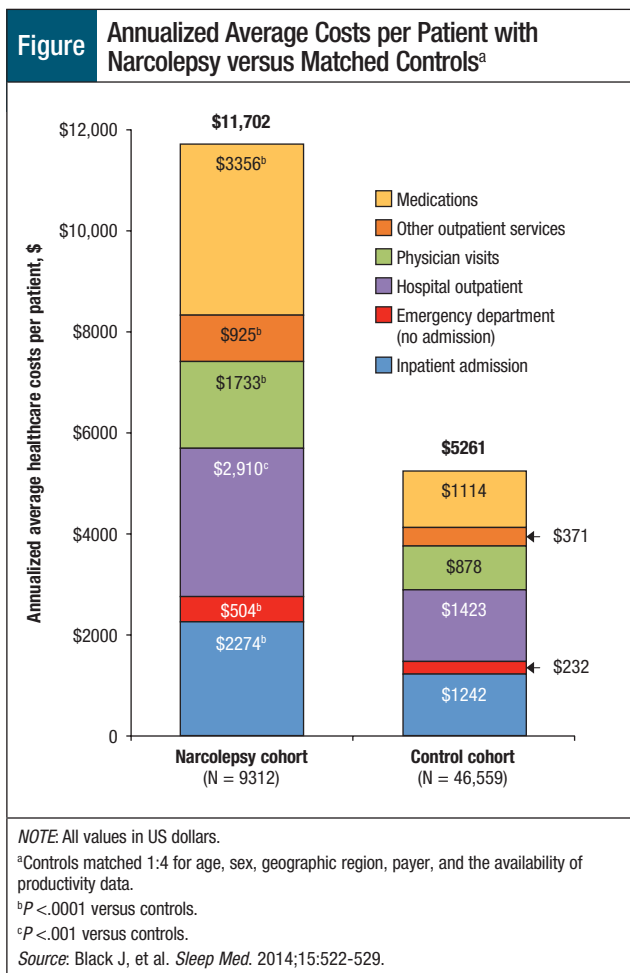
Although narcolepsy has an early onset, a diagnostic delay that often exceeds 10 years from the time of symptom onset has consistently been reported in the literature,<sup>29</sup> suggesting that narcolepsy is underrecognized and underdiagnosed. This delay may result from several factors, including lack of clinician recognition of the signs and symptoms of narcolepsy, leading to multiple physician visits before receiving a diagnosis<sup>30-33</sup>; lack of easily measurable and reliable biomarkers for diagnosis; as well as misdiagnosis of narcolepsy as another condition, such as epilepsy, depression, or attention-deficit/hyperactivity disorder, which further delays treatment.<sup>31,33-35</sup>

Misdiagnosis is especially relevant in pediatric narcolepsy, because narcolepsy in children may present as excessive sleepiness with or without facial grimaces or hypotonia, weight gain, and poor attention, which differs from the presentation of narcolepsy in adults and can result in inappropriate treatment.<sup>34-36</sup> In addition, misdiagnosis in children carries the consequences of delaying psychosocial development or promoting low academic achievement in children who could improve with appropriate treatment for narcolepsy.<sup>23</sup>

A diagnosis delay affects the disease-related burden: earlier onset and earlier diagnosis have been associated with better outcomes; for example, patients diagnosed before age 30 years have reported less unemployment and better health perception than those diagnosed after age 30.<sup>37</sup> Thus, timely diagnosis is important from the patient’s perspective, as well as for managed care. Relevant diagnostic testing represents an appropriate focal point for improving patient management.

In addition to clinicians’ lack of symptom recognition, which can be improved through education initiatives to expand symptom awareness, a barrier to diagnosis is the lack of readily available and accurate biomarkers and diagnostic tests for narcolepsy, especially in the absence of cataplexy. The diagnostic challenges of narcolepsy in the absence of cataplexy are well-recognized,<sup>4</sup> and recent revisions to the *International Classification of Sleep Disorders—Third Edition (ICSD-3)* and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* diagnostic criteria have attempted to account for these differences in presentation.<sup>3,38</sup> In particular, the *ICSD-3* distinguishes between 2 types of narcolepsy.

Type 1 narcolepsy is defined based on the actual or presumed loss or reduction of hypocretin and is characterized by the presence of cataplexy or a reduction in measured CSF hypocretin-1 level, with positive evi-



dence from electrophysiologic sleep studies also included as a potential diagnostic indicator.<sup>3</sup>

Type 2 narcolepsy is determined by the absence of cataplexy and, when a lumbar puncture is performed, by normal CSF hypocretin levels, with the diagnosis primarily dependent on electrophysiologic tests,<sup>3</sup> such as nocturnal polysomnography and the Multiple Sleep Latency Test (MSLT). In contrast to the *ICSD-2*,<sup>39</sup> the *ICSD-3* endorses a greater reliance on biomarkers and electrophysiologic testing than symptom recognition.<sup>3</sup> Whereas earlier *ICSD* classifications allowed for a diagnosis of narcolepsy based on clinical features, including reported cataplexy, without the biomarkers of electrophysiology or low CSF hypocretin levels, such testing is required for diagnosis according to *ICSD-3*, even in the case of a history of cataplexy.<sup>3</sup> The reason for this change is the limitations involved in making a clinical diagnosis of cataplexy, which is largely a patient-reported symptom that is rarely witnessed by the clinician and can be subject to mistaken recognition or lack of awareness of symptoms by the patient.<sup>3</sup> The main features of the 2

**Table 1** Main Clinical Features of Narcolepsy Type 1 and Type 2 versus Idiopathic Hypersomnia

Features	Narcolepsy type 1 <sup>2-4,41,49</sup>	Narcolepsy type 2 <sup>2-4,41,49</sup>	Idiopathic hypersomnia <sup>40</sup>
Main symptoms	Chronic sleepiness (>3 mo), cataplexy	Chronic sleepiness (>3 mo)	Chronic sleepiness (>3 mo)
Ancillary symptoms (REM sleep phenomena)	Hypnagogic/hypnopompic hallucinations, sleep paralysis, dream features	Hypnagogic/hypnopompic hallucinations, sleep paralysis, dream features	No abnormal REM phenomena
Age of onset, yrs	Median, 16	Median, 16	Mean, 21.8 <sup>41</sup>
Pathophysiology	Low to absent hypocretin cells (>85% loss)	Presumed low hypocretin cells (<85% loss)	Unknown, possibly low hypocretin cells
CSF hypocretin level	Low to absent	Usually normal	Usually normal
ESS score	>10, mean 16	>10, mean 16	>10, mean 16
Diagnostic test	PSG + MSLT	PSG + MSLT	PSG + MSLT
Diagnostic features: PSG	RLat <15 min in 50% of patients	RLat <15 min in some patients	Normal RLat
Diagnostic features: MSLT	Mean sleep latency ≤8 min ≥2 SOREMPs	Mean sleep latency ≤8 min ≥2 SOREMPs	Mean sleep latency ≤8 min <2 SOREMPs
First-line treatment options	Sodium oxybate, modafinil/armodafinil	Sodium oxybate, modafinil/armodafinil	Modafinil/armodafinil <sup>a</sup>
Second- and third-line treatment options	Methylphenidate, amphetamines	Methylphenidate, amphetamines	Methylphenidate, amphetamines
Common misdiagnoses	Depression, sleep apnea, epilepsy	Depression, sleep apnea	Depression, sleep apnea

<sup>a</sup>Not approved by the US Food and Drug Administration for this indication. CSF indicates cerebrospinal fluid; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; PSG, polysomnography; REM, rapid eye movement; RLat, rapid eye movement sleep latency; SOREMPs, sleep-onset rapid eye movement periods.

types of narcolepsy compared with idiopathic hypersomnia are shown in **Table 1**.

In contrast to the *ICSD-3* criteria,<sup>3</sup> the *DSM-5* criteria recognize narcolepsy based on meeting at least 1 of 3 nonoverlapping criteria (ie, history of cataplexy, hypocretin deficiency, and positive evidence on polysomnography), in addition to excessive sleepiness for ≥3 months.<sup>38</sup>

The role of hypocretin deficiency in type 1 narcolepsy may potentially be perceived as enabling a more accurate diagnosis, even in the absence of cataplexy; however, CSF hypocretin testing lacks a standardized, readily available assay and is an invasive diagnostic test.

In the absence of reported cataplexy, and with negative electrophysiologic findings for type 2 narcolepsy, the presence of severe excessive daytime sleepiness usually leads to a diagnosis of idiopathic hypersomnia if other causes of excessive daytime sleepiness are excluded and if the MSLT demonstrates a mean sleep latency of ≤8 minutes.<sup>3,40</sup> Idiopathic hypersomnia can be as disabling as narcolepsy and can evolve into type 1 or type 2 narcolepsy.<sup>41,42</sup>

The evolution of narcolepsy also has been suggested by postmortem data from a patient with narcolepsy without cataplexy, but having the HLA-DQB1\*0602 geno-

type, showing only a 33% loss of hypocretin neurons, in contrast to a >90% loss of neurons in type 1 narcolepsy.<sup>43</sup> In this regard, the correlation of CSF hypocretin deficiency with HLA-DQB1\*0602 indicates that assessment of serum HLA-DQB1\*0602 by using a less invasive test may be of value as an alternative to or before CSF assessment, as is also suggested by the *DSM-5*<sup>38</sup>; however, the results from such a test should be considered indicative rather than conclusive, because 26% of the normal population are positive for HLA-DQB1\*0602.<sup>44</sup>

Although cataplexy is the sole pathognomonic symptom for narcolepsy and is present in a majority of patients with narcolepsy,<sup>2</sup> many patients have excessive daytime sleepiness as their main symptom. Excessive daytime sleepiness may be debilitating, and it also can be caused by several sleep disorders, such as chronic sleep deprivation or obstructive sleep apnea syndrome.<sup>3</sup> The presence of ancillary symptoms of narcolepsy, such as hypnagogic hallucinations, automatic behavior, excessive and unusual dreaming, and sleep paralysis, can help establish a presumptive clinical diagnosis that can lead to the ordering of appropriate confirmatory biomarker tests.

The barriers that can unduly delay the treatment of narcolepsy include a requirement for positive diagnostic biomarkers. The strongest rationale for objective testing is the presence of chronic sleepiness and the absence of cataplexy in the presence of other narcolepsy-related symptoms; the value of nocturnal polysomnography followed by daytime MSLT in this situation should be recognized without restrictions. Practice parameters for these tests have been developed.<sup>45,46</sup>

The appropriate use of diagnostic tests provides additional objective support of a narcolepsy diagnosis in the presence of cataplexy, reducing the chance of a false-positive result if relying exclusively on the patient-reported presence of cataplexy. Although these tests have clinical utility in the pediatric population, their specificity and sensitivity in children and adolescents remain to be defined; this indicates that symptomatic presentation is the most useful diagnostic indicator in children, albeit not always an accurate one, and that the need for and choice of tests should be individualized, depending on their availability and utility in pediatric patients.

Additional diagnostic considerations are that negative objective tests for narcolepsy are not always conclusive, especially because of the limitations of the MSLT and the variability in how it may be performed<sup>21-26</sup>; the MSLT is the primary objective test in both sets of diagnostic criteria. A correct interpretation of the MSLT requires a polysomnography to be performed on the previous night. Normative data are well-established in adult populations, but the key limitations of the MSLT include the lack of adequate normative data in pediatric



**Table 2 Medications Available in the United States for the Treatment of Narcolepsy and Their Relevance to Patient Management in a Managed Care Setting**

Drug/drug class	FDA-approved indication for narcolepsy?	AASM treatment recommendations <sup>48</sup>	Clinical considerations	Managed care considerations
Antidepressants, including SSRIs, SNRIs, TCAs	No	Cataplexy; option for hypnagogic hallucinations and sleep paralysis	Data on efficacy primarily limited to case reports; associated with side effects that may include precipitation of other sleep-related disorders, anticholinergic effects, and rebound cataplexy	May have low drug acquisition costs; side effects can increase costs if not prescribed appropriately <sup>a</sup>
Amphetamine salts (Adderall, but not Adderall XR)	Yes: narcolepsy general indication	Daytime sleepiness	Lack of evidence for efficacy other than daytime sleepiness; abuse potential; side effects may include growth suppression in children	May have low drug acquisition costs; third-line therapy; restricted to a single narcolepsy symptom
Methamphetamine (Desoxyn)	No	Daytime sleepiness	Lack of evidence for efficacy other than daytime sleepiness; abuse potential; side effects may include growth suppression in children	May have low drug acquisition costs; third-line therapy; restricted to a single narcolepsy symptom <sup>a</sup>
Dextroamphetamine sulfate (Dexedrine)	Yes: narcolepsy general indication	Daytime sleepiness	Lack of evidence for efficacy other than daytime sleepiness; abuse potential; side effects may include growth suppression in children	May have low drug acquisition costs; third-line therapy; restricted to a single narcolepsy symptom
Lisdexamfetamine (Vyvanse)	No	Daytime sleepiness	Lack of evidence for efficacy other than daytime sleepiness; abuse potential; side effects may include growth suppression in children	May have low drug acquisition costs; considered a third-line therapy; restricted to a single narcolepsy symptom <sup>a</sup>
Methylphenidate HCl (Ritalin, Concerta, Methylin, Equasym XL)	Yes: narcolepsy general indication	Daytime sleepiness	Lack of evidence for efficacy other than daytime sleepiness; abuse potential; side effects may include growth suppression in children	May have low drug acquisition costs; second-line therapy; restricted to a single narcolepsy symptom
Armodafinil (Nuvigil)	Yes: excessive sleepiness in narcolepsy	Developed subsequent to the guidelines	No demonstrable effect on other narcolepsy symptoms; side effects include rare but severe rash in children, reduction in oral contraceptive efficacy	First-line therapy; restricted to a single narcolepsy symptom
Modafinil (Provigil)	Yes: excessive sleepiness	Daytime sleepiness	No demonstrable effect on other narcolepsy symptoms; side effects include rare but severe rash, and reduction in oral contraceptive efficacy	First-line therapy; restricted to a single narcolepsy symptom
Sodium oxybate (Xyrem)	Yes: excessive sleepiness and cataplexy	Cataplexy, daytime sleepiness, and disrupted sleep; option for hypnagogic hallucinations and sleep paralysis	Need for individualized dose titration; sedative drug interactions; generally well-tolerated but side effects may include parasomnias; high salt content may limit its use in salt-restricted patients	High drug acquisition costs; first-line therapy approved for the 2 primary symptoms of narcolepsy, and recommended, but not approved, for treatment of other symptoms; central pharmacy distribution

<sup>a</sup>Not approved by the FDA for the treatment of narcolepsy.

AASM indicates American Academy of Sleep Medicine; FDA, US Food and Drug Administration; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; XL, modified release; XR, extended-release.

Adapted with permission from Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. *Sleep Med.* 2015;16:9-18.

populations and the presence of confounding factors, such as the use of some medications and the presence of other medical and psychiatric disorders, including anxiety, that may affect the outcomes.

Although patients with narcolepsy may display negative objective diagnostic findings, the consequences of symptoms are nevertheless disabling, and patients presenting with symptoms and other characteristics consistent with narcolepsy should be started with appropriate therapy and the testing repeated at a later date, as recommended by the ICSD-3.<sup>3</sup>

**Treatment Considerations**

Although behavior modification, such as maintaining nocturnal sleep hygiene and regular scheduling of daytime naps, may slightly improve daytime function in patients with narcolepsy, disease management relies on pharmacologic therapy, which is primarily symptomatically driven. Practice parameters for the treatment of

narcolepsy have been developed, including one set by the European Federation of Neurological Societies<sup>47</sup> and the other by the American Academy of Sleep Medicine,<sup>48</sup> with recommendations that include approved drugs, as well as some drugs that are not approved but have demonstrated at least some evidence of efficacy. More recently, practical recommendations have been published to provide further clinical guidance on the appropriate use of pharmacologic therapies, including specifically in pediatric patients,<sup>49-51</sup> because pediatric treatment guidelines have not been developed.

**Drug Therapy**

In the United States, several drugs are approved by the US Food and Drug Administration (FDA) for the treatment of specific symptoms of narcolepsy, and additional drugs may be effective for some symptoms but are not currently approved by the FDA for the treatment of the disease (Table 2).

Stimulants such as methylphenidate, amphetamines, and modafinil and its enantiomeric derivative armodafinil are FDA approved only for excessive daytime sleepiness in narcolepsy. Methylphenidate and amphetamines predate the use of modafinil or armodafinil, and although they are less costly than the newer drugs, they are associated with a potential for abuse, as well as side effects that include growth suppression in children and cardiovascular disease in adults<sup>52,53</sup>; these drugs are considered second-line (methylphenidate) or third-line (amphetamines) therapy.

Modafinil and armodafinil are FDA approved for the treatment of excessive daytime sleepiness associated with narcolepsy, and may be considered first-line therapy, although neither of these drugs is effective or approved as monotherapy for other narcolepsy symptoms.<sup>54,55</sup> Sodium oxybate is FDA approved for excessive daytime sleepiness and cataplexy in adults with narcolepsy.<sup>56</sup> The clinical considerations of modafinil and armodafinil also include their association with severe rashes, notably in children, although these are rare occurrences, and their potential for reducing the efficacy of oral contraceptives.<sup>54,55</sup>

Sodium oxybate is a central nervous system (CNS) depressant that is the sodium salt of gamma hydroxybutyrate, which is an endogenous metabolite of gamma-aminobutyric acid. It is the only medication in the United States currently approved by the FDA for the treatment of excessive daytime sleepiness and cataplexy associated with narcolepsy, for which it is considered first-line therapy<sup>48</sup>; it is also the only medication recommended in the American Academy of Sleep Medicine and European Federation of Neurological Societies guidelines for the treatment of all the symptoms of narcolepsy.<sup>47,48</sup> Sodium oxybate is a CNS depressant, and concurrent use with alcohol and sedative hypnotics are contraindicated.<sup>56</sup> The common side effects of sodium oxybate include nausea and/or vomiting, headache, dizziness, and somnolence.<sup>56,57</sup>

Sodium oxybate is a Schedule III controlled substance with a requirement of central pharmacy dispensing to mitigate the risks for serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion.<sup>56</sup> Sodium oxybate requires titration over a period of several weeks, and, therefore, sufficient time should be allowed for a response.<sup>58</sup> Clinically meaningful improvements in excessive daytime sleepiness and cataplexy were observed in most patients within 2 months of taking sodium oxybate. The maximum response required a median of approximately 3.5 months for excessive daytime sleepiness and 7 months for cataplexy.<sup>58</sup>

Based on what is considered level 1 evidence from adequately designed, randomized, controlled trials, the American Academy of Sleep Medicine treatment parameters currently recommend the use of modafinil for daytime sleepiness, and sodium oxybate for daytime

sleepiness, cataplexy, and disturbed sleep as standard therapies for patients with narcolepsy.<sup>48</sup> Other treatment recommendations (non-level 1) for specific symptoms also include antidepressants, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants, which may be used for the treatment of cataplexy, sleep paralysis, and hypnagogic hallucination.<sup>48</sup>

However, these drugs are not FDA approved for the treatment of narcolepsy, and there is less of an evidence base for their efficacy than for first-line or FDA approved drugs for narcolepsy.<sup>48</sup> Furthermore, the withdrawal of antidepressants may result in rebound cataplexy,<sup>59</sup> and antidepressants, such as tricyclic antidepressants, are also associated with well-recognized anticholinergic effects, including dry mouth, blurred vision, sweating, constipation, tachycardia, weight gain, hypotension, difficulty in urinating, and impotence.<sup>47</sup>

As emphasized in the practical recommendations,<sup>49-51</sup> no single management strategy is available for initiating treatment for narcolepsy. Therefore, treatment decisions should be customized based on clinician-patient discussions regarding the symptoms, needs, and goals of individual patients (Tables 1 and 2). The choice of therapy will depend on a variety of factors related to the disease, the medication, and the patient.

Disease-related factors to consider include whether single or multiple symptoms are present, either patently or elicited from discussions with the patient and his or her spouse/caregiver, as well as the primary symptomatic complaint, which may not necessarily be the same as the main presenting symptom.

Medication characteristics that may affect treatment choice are drug-drug interactions, especially in the presence of comorbidities or the need for polypharmacy as a result of multiple narcolepsy symptoms, adverse-event profile, and the titration of dosing regimen, because a more convenient dosing regimen is likely to result in greater adherence to therapy.

Patient-related considerations include the patient's age and lifestyle, with the latter reflecting daily activities and family, as well as lifestyle or substance use, such as nicotine, alcohol, caffeine, and cannabis, all of which should be realistically discussed, especially with adolescent patients.

### **Balancing Narcolepsy Treatment Needs with Cost Containment: A Managed Care Perspective**

In the much-needed current climate of cost containment, strategies for managing costs may focus on the per-unit drug costs rather than on the overall healthcare costs. However, the total healthcare costs and resource utilization may provide a more relevant metric than drug acquisition costs when evaluating the balance between

the cost of care and quality of care of patients with narcolepsy. Although the use of less costly drugs may result in short-term savings to the pharmacy budget, this approach may compromise patient outcomes and could have the unintended effect of increasing associated medical utilization and costs. In addition, pharmacy costs often represent a small proportion of the overall healthcare costs; in narcolepsy, medications only account for approximately 28% of the total healthcare costs.<sup>11</sup>

Thus, managed care policies for narcolepsy should minimize barriers to appropriate and effective care to allow patients with this disabling disease to return to the highest level of functioning. With the current range of medications available, treatment decisions should reflect effective management of complex clinical issues rather than solely medication cost considerations. **Table 3** summarizes considerations in narcolepsy and provides management recommendations for managed care.

Managed care policies that encourage regular patient assessment (follow-up), especially during the early stages of treatment initiation when follow-up may need to be frequent until efficacy and tolerability of a particular therapy are established, will aid in achieving benefits. While this may initially increase resource utilization and costs, over the long-term it can help stabilize the treatment modality and help patients reach their therapeutic goals.

The majority of the medications for narcolepsy require careful titration of dose to achieve the right balance between efficacy and side effects. Patients are also likely to have multiple symptoms, and the costs of treatment, whether with a single, more expensive drug for multiple symptoms or the use of polypharmacy with less costly medications, should be balanced against the long-term risks and benefits of each treatment.

**Conclusions**

Although narcolepsy has a low prevalence, it is associated with a substantial socioeconomic burden resulting from high direct and indirect costs and reductions in patient functioning, as well as early disease onset, lack of cure, and a need for lifelong therapy.

Managed care policies could help alleviate the economic burden associated with narcolepsy management, as well as its clinical burden, by supporting the development of evidence-based protocols that include a clinician’s ability to make treatment decisions and to shorten the time required to find an effective treatment plan. Such policies balance long-term patient and economic benefits against short-term cost-savings. The best policies are those that are founded on the current treatment guidelines for narcolepsy.

Clinician–patient decisions for individualizing diagnostic and treatment choices as suggested in best practice recommendations for narcolepsy are also important. In

**Table 3** Narcolepsy: Considerations and Recommendations for Managed Care

<b>Disease considerations</b>
Narcolepsy is a rare, lifelong, incurable disabling, neurologic disorder that typically begins in childhood (median age at onset, 16 years)
Produces impaired psychosocial development, education, and employment, and often results in permanent disability and increased mortality
High burden of illness associated with its comorbidities, increased mortality, and high healthcare utilization and associated costs
Diagnosis is often delayed by 8-15 years because of limitations in accuracy and availability of diagnostic biomarkers
Symptoms develop over time; initial diagnostic tests may be falsely negative despite severe and specific clinical signs and symptoms
Excessive sleepiness in the absence of cataplexy can be just as debilitating and disabling as narcolepsy with cataplexy, into which it can evolve
<b>Recommendations to reduce morbidity associated with narcolepsy and its symptoms</b>
Medication treatment should be initiated as soon as the disorder is suspected (usually based on the reported presence of cataplexy) even before a definitive diagnosis is established, primarily because of safety concerns
Therapy should be made available without limitations, such as prior authorization for anything other than diagnosis or suspected diagnosis of labeled indication, or step therapy, which can delay treatment and increase morbidity
Multiple concurrent medications should be considered and may be required using a therapeutic approach that needs to be individualized, with appropriate drug titration over time to prevent tachyphylaxis, abuse, and adverse effects
Older narcolepsy medications, such as methylphenidate and amphetamines, should be regarded as second- or third-line treatment options because of their potential for abuse, severe adverse effects, and growth suppression in children

general, managed care policies should take into consideration the clinical manifestations of narcolepsy and the complexity of its diagnosis and treatment. Identifying the optimal treatment regimen for the individual patient is key to helping maximize work productivity, daily functioning, and overall quality of life in patients with this condition. ■

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## STAKEHOLDER PERSPECTIVE

## Improved Diagnosis and Treatment of Narcolepsy May Also Help to Reduce the Associated Costs

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**PAYERS:** Narcolepsy receives a reasonable degree of awareness and attention in the managed care pharmacy area, primarily as a result of the drugs used as standard-of-care treatments. For many years, stimulants offered the only treatment option for narcolepsy and were monitored for their abuse potential. Modafinil and armodafinil offered newer mechanisms of action at a much higher cost compared with traditional amphetamine or methylphenidate preparations. Recently, generic versions of these agents have been launched, which reduces their cost to \$200 to \$500 monthly versus their branded equivalents at \$700 to \$2300 monthly. Sodium oxybate has remained the standard treatment for patients with narcolepsy, at costs that exceed \$10,000 for a standard 30-day supply. Any drug that costs more than \$100,000 annually is going to prompt health plans to apply some level of management to ensure that only appropriate patients have access to it.

Although Thorpy and colleagues propose open access for the use of drugs for this disease,<sup>1</sup> the challenge for the managed care pharmacy management team is in managing a drug budget that is increasingly becoming more difficult to control. With narcolepsy, health plans may resort to utilization management tools that are designed to drive appropriate use and promote lower-cost alternatives when they are available.

The costs of many years of misdiagnosis or inappropriate resource utilization are major concerns to health plans that are paying for these services.<sup>2</sup> In addition, the doubling of direct costs to patients with narcolepsy compared with controls without the disease speaks to the need for health plans to assist in the management of these patients; however, these costs pale in comparison with the cost of the drugs to treat narcolepsy. In other words, a cost offset does not exist in narcolepsy, which significantly affects pharmacy spending on the population with narcolepsy.

The lack of easily measurable and reliable biomarkers also adds to the challenge of managing patients with this disease.<sup>3-6</sup> Health plans resort to more brute force techniques, including prior authorizations with prescribing limits to specialty physicians, attestation of diagnosis,

step-edits through lower-cost or generic options, and re-authorizations to determine if a drug is providing a clinical benefit for the patient. In some cases, reauthorization is an attempt to ensure that a diagnosis is correct.

Cataplexy is a defining symptom of narcolepsy; however, in the presence of excessive daytime sleepiness alone, health plans struggle with this symptom, being concerned that patients without narcolepsy may be misdiagnosed and medications will be prescribed for patients inappropriately.

**PROVIDERS:** Educating providers could play an important role in the identification and accurate diagnosis of narcolepsy. Educating the health plan pharmacy management team may also be appropriate, because new drugs for narcolepsy have not been launched for several years. It is important to provide a refresher on the latest approaches to the diagnosis and treatment of rare diseases. This has recently been a key point in diseases such as gout and congestive heart failure, as agents were approved after decades without any new treatment options approved by the US Food and Drug Administration.

There is a need for a disease-modifying treatment option in narcolepsy, as well as for drugs with a reasonable cost and good safety and tolerability profiles. Health plans will not be resistant when a patient can be effectively diagnosed and physicians can prescribe a treatment that is appropriate and best-suited for a patient. Today's managed care pharmacy benefit, however, requires that reasonable utilization management tools be used in an attempt to control spending and allow for additional dollars to be spent on newer, and often breakthrough medications, to be added to coverage for a multitude of disease states. ■

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