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REVIEW ARTICLE

Narcolepsy: Beyond the Classic Pentad

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Abstract
Narcolepsy is a rare, disabling, chronic neurologic disorder that requires lifelong management of symptoms with pharmacologic and nonpharmacologic methods. The pentad symptoms of narcolepsy include excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep paralysis, and hypnagogic/hypnopompic hallucinations. However, people with narcolepsy often experience additional symptoms and disability related to nonpentad symptoms and comorbidities, such as cognitive, psychiatric, metabolic, and sleep disturbances. Current treatment strategies have focused primarily on addressing two of the pentad symptoms, excessive daytime sleepiness, and cataplexy, mainly owing to medication options being approved by the US Food and Drug Administration for these specific indications, neglecting the full 24-h impact and spectrum of symptoms. Meanwhile, the burden of disease extends far beyond these symptoms, and optimal management should reflect a comprehensive, patient-specific approach that not only addresses the entire pentad, but also goes beyond it to include the complete clinical presentation and manifestations of the disease. Individualized treatment must consider the patient's age and stage of life, most debilitating symptoms, support system and structure, comorbid conditions, treatment goals, and overall health. This review discusses care considerations for people living with narcolepsy in the context of their clinical characteristics beyond the hallmark features of narcolepsy.

Key Points

People with narcolepsy often experience clinical disturbances and comorbid conditions outside of the classic pentad of symptoms, which includes excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep paralysis, and hypnagogic/hypnopompic hallucinations.

Lifelong management of narcolepsy is required and should include an individualized treatment approach that considers the patient's age and lifestyle, most debilitating symptoms, comorbidities, valued support systems, specific treatment goals, and overall health.

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1 Introduction

Narcolepsy is a rare, disabling, chronic neurologic disorder that affects approximately 1 in 2000 people [1] and impedes optimal health, function, and quality of life across the 24-h cycle [2]. The primary pentad symptoms include excessive daytime sleepiness (EDS), disrupted nighttime sleep (DNS), sleep paralysis, hypnagogic and hypnopompic hallucinations, and cataplexy [3–5]. Severity of symptoms can vary significantly between individuals with narcolepsy, and patients may not present with the full set of pentad symptoms [6]. Severe EDS is commonly the presenting concern; however, other reasons for evaluation have included attention difficulties,[2, 3, 7] poor school or work performance, hallucinations, recurrent sleep paralysis, and cataplexy [6]. Cataplexy, an abrupt involuntary change in muscle tone during wakefulness, is pathognomonic to narcolepsy type 1 (NT1) but may be underdiagnosed owing to subtle variations in phenotype [3, 8, 9]. Patients may also experience automatic behaviors, a common auxiliary symptom of narcolepsy [2, 3, 7], in which they unknowingly complete tasks or activities while appearing awake [3, 7, 10].

Lifelong management of narcolepsy is required [5], underscoring the need to re-evaluate and evolve treatment expectations and goals over time on the basis of clinical

status and expected age-related changes, such as overall health, sleep changes, maturity, progressive independence, and social expectations and obligations [5, 11–13].

NT1 is characterized by signs of rapid eye movement (REM)-sleep dissociation, most specifically cataplexy, and/or low levels of orexin A in cerebrospinal fluid (CSF), likely owing to marked and selective loss of orexin-producing neurons in the lateral hypothalamus [1, 10, 14–17]. If there is clinical history of cataplexy, diagnosis of NT1 or NT2 can be made clinically using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria, Text Revision (DSM-V-TR), or alternatively with the International Classification of Sleep Disorders, Third Edition, Text Revision (ICSD-3-TR), with either CSF orexin A deficiency or findings of a mean sleep latency ≤ 8 min and ≥ 2 sleep-onset REM periods (SOREMPs; REM sleep within 15 min of sleep onset) on a multiple sleep latency test (MSLT) [10, 18]. A SOREMP on the preceding nocturnal polysomnogram is now included as a standalone diagnostic criterion for NT1, as opposed to prior criteria that only allowed for it to be included as a substitution for one of the SOREMPs identified with the MSLT [19].

The exact cause of the orexin deficiency is unknown but is likely attributable to autoimmune dysfunction [1, 14]. The human leukocyte antigen (HLA) -*DQB1*06:02* allele is a known risk factor for narcolepsy and has been detected in > 98% of people with NT1 [1, 14]. Orexin A and orexin B are implicated in a wide variety of physiologic functions including, but not limited to, sleep-wake cycles, temperature regulation, cardiovascular outputs, hormonal regulation, energy homeostasis and metabolism, feeding and appetite, and reward systems [20–24]. Both orexin A and orexin B selectively bind to the orexin 1 and orexin 2 receptors; however, orexin B has an approximately ten times greater affinity for the orexin 2 receptor [25], an important component of the regulation of sleep and wakefulness [26]. Activation of glucagon-like peptide 1 receptors, which increases satiety and reduces food intake, has been associated with pre- and postsynaptic modulation of orexin [27], further supporting the role of orexin in feeding behaviors [28]. Orexin A enables sustained wakefulness by stimulating wake-promoting regions in the cortex, brain stem, and basal forebrain [1]. Orexin A-expressing neurons are also part of a neural pathway that regulates autonomic responses to strong positive emotions; an imbalance can impact control of motor neurons and brain regions that promote REM sleep [1].

In contrast, narcolepsy type 2 (NT2) is defined by absence of cataplexy and normal CSF levels of orexin A, if measured [10]. The underlying pathophysiology of NT2 is not well understood, although less extensive loss or functioning of orexin-producing neurons may contribute [1, 14, 16]. Though less prevalent than in NT1, *HLA-DQB1*06:02* genetic polymorphism may play a role, with a higher incidence among patients with NT2 (~ 50%) compared with the general population (12−30%) [1]. Assessment of orexin CSF concentrations requires a lumbar puncture, which may not be routinely performed owing to a variety of factors such as lack of access to testing or potential risks [12, 29, 30]. There have been reports of normal orexin levels in some patients with NT1 or low orexin levels in some patients with NT2. Diagnosis from NT2 to NT1 subtypes may change based upon the patient's evolving clinical presentation or identification of CSF orexin A deficiency [29, 31, 32].

The onset of narcolepsy symptoms typically peaks in adolescence at a mean age of 15 years; however, diagnosis is typically delayed and can be complicated by lack of symptom recognition and misdiagnoses [33, 34]. As most patients develop symptoms during adolescence or young adulthood, earlier and improved screening may prevent delayed diagnosis and treatment, potentially resulting in better outcomes [1, 6, 35, 36]. Pediatric narcolepsy can have substantial burden on psychosocial development, negatively affecting academic performance, behavior, mental health, and social relationships [5, 30].

Similar to other chronic illnesses, including mental health [37] and autoimmune disorders [38], women with narcolepsy often experience a longer diagnostic delay compared with men [39], suggesting that sex may influence time to diagnosis. In preclinical and clinical studies, sex-based differences have also been observed in narcolepsy phenotype [40, 41]. In a cross-sectional study of patients with NT1, an analysis of baseline data of approximately 200 men and women revealed that significantly more women reported automatic behaviors (55.4% versus 40.0%; $P < 0.05$), had higher Epworth Sleepiness Scale score (median score, 10.0 versus 9.0; $P < 0.05$), and had higher Beck Depression Inventory scores (median score, 10.5 versus 5.0; $P < 0.001$) [41]. A trend toward more severe symptom burden based on the Narcolepsy Severity Scale (median score, 19 versus 18; $P = 0.057$) was also observed for women. At this time, the underpinnings for these gender differences are unknown. However, the longstanding recognition of the inverse relationship between orexin and the hypothalamopituitary gonadal axis [42], combined with menstrual cycle guided changes to prepro-orexin mRNA, orexin peptide, and the quantity of orexin receptors in specific brain regions, are likely relevant [43].

Current treatment options for narcolepsy include pharmacotherapy and behavioral approaches, which include psychology services, social support, and lifestyle modifications [35, 44, 45]. As there is no cure, pharmacologic treatment, often with multiple medications, is typically focused on control of symptoms associated with the classic pentad, particularly EDS and cataplexy [46, 47]. US guidelines [American Academy of Sleep Medicine (AASM)] have classified sodium oxybate (SXB), modafinil, pitolisant,

and solriamfetol as strong recommendations for treatment of EDS symptoms; this recommendation is based on systematic review of available evidence, implying that almost all patients should receive the recommended therapies and adherence may be used as a quality or performance measure [48]. Armodafinil, dextroamphetamine, and methylphenidate have conditional recommendations for EDS on the basis of available evidence, implying most patients should receive the suggested treatment if determined to be clinically appropriate and aligned with individualized patient preferences [48]. Only SXB and pitolisant hold strong recommendations for treatment of cataplexy according to the AASM [48]. EU guidelines (European Academy of Neurology, European Sleep Research Society, and European Narcolepsy Network) have also been developed, utilizing a Patients-Intervention-Comparator-Outcome framework to formulate expert opinion statements [4]. EU guidelines strongly recommend SXB, modafinil, pitolisant, and solriamfetol for EDS symptoms in adults [4]. SXB received a strong recommendation and pitolisant received a weak recommendation for treatment of cataplexy [4]. Notably, SXB is the only monotherapy recommended as first-line treatment if EDS, cataplexy, and DNS are present [4]. Since the initial approval of twice-nightly SXB in 2002, additional oxybates have been approved for treatment of narcolepsy, including a twice-nightly oral solution of mixed-salt oxybates, containing calcium, magnesium, potassium, and sodium [49], and an extended-release, once-nightly formulation of SXB [50]. Antidepressants are not approved for narcolepsy treatment, but may be used—and may even be required by payors—to treat cataplexy off-label [46]; however, the 2021 AASM clinical practice guidelines did not include antidepressants owing to lack of evidence [48]. Treatment options with some evidence of efficacy for sleep paralysis and hypnagogic/hypnopompic hallucinations include SXB and antidepressants [4, 51].

Utilizing different medications with complimentary mechanisms of action to target symptoms may be beneficial, potentially allowing for lower drug dosages and fewer side effects while still maintaining efficacy [47]. Ultimately, treatment decisions regarding medication regimen should be made collaboratively with the patient and consider their individualized characteristics, such as age, symptoms, needs, goals, and lifestyle [5]. For some patients, drug regimens that are more complex and require multiple doses per day may result in nonadherence and add to the overall burden experienced with the disorder [52]. Ongoing evaluation of efficacy and tolerability of therapies is necessary to better inform and optimize the management plan [47]. If there is an observed change in the regimen's therapeutic efficacy, it may not be owing to changes in medication response or tolerability. Clinicians should assess if there are challenges with adherence and/or changes in patients' daily life, such as stressful life events, which may exacerbate their symptoms. Input from a patient's caregiver or family member may be a useful resource in determining observed benefit or lack of benefit of treatment [47].

Nonpharmacologic strategies, such as behavioral, psychological, lifestyle, diet, and social support, should always be considered and are often used in conjunction with medications to gain better control of symptoms, mitigate negative side effects, and improve adherence to the drug regimen [53]. Behavioral interventions include patient education, improved sleep hygiene, scheduled naps, cognitive behavioral therapy, routine patient self-assessments, manipulation of skin and body temperature, and use of community and advocacy group resources, such as support groups, to address the psychosocial burden of narcolepsy (Table 1) [44]. Peer support, which can occur at the individual or group level, is another invaluable strategy for people with narcolepsy (PWN) [53, 54]. Peer support is when people use their own lived experiences to support others with shared experiences, providing a space to feel accepted and understood and to treat everyone's experiences, even when different, as being equally important [53–55].

While current treatment paradigms often only focus on EDS and cataplexy, optimal management of narcolepsy requires a comprehensive and individualized approach. Characterization of the pentad and non-pentad symptoms, comorbidities, and associated burden is necessary to identify individualized treatment goals. In addition, these factors should be considered during treatment selection and when providing anticipatory guidance of potential benefit, time to improvement, as well as possible side effects. In this review, we explore whole person care considerations for PWNs in the context of their clinical characteristics beyond the hallmark features of narcolepsy.

2 Symptoms and Features Beyond the Pentad

In addition to the classic pentad, PWN may experience other clinical symptoms and associated features, such as cognitive, psychiatric, metabolic, and sleep disturbances, over time (Fig. 1) [3]. There is no consensus on why these disturbances arise in narcolepsy. They may be the result of hypothalamic dysfunction, EDS, psychosocial burden of illness, or medication side effects. Common etiologic factors may also underlie the concordance of narcolepsy with other illnesses/comorbidities. Notably, sleep clinicians may care for individuals with narcolepsy from adolescence through a geriatric stage, and the symptoms, clinical needs, and comorbidities of patients may evolve over time.

Table 1. Nonpharmacologic and behavioral strategies for narcolepsy

Strategy	Description
Psychotherapy [3]	Counseling to address psychiatric symptoms and impact of narcolepsy
Diet and exercise [3, 54, 124]	Regular physical activity, strategic caffeine intake, and a balanced, low-carbohydrate diet
Napping [47, 124]	Planned and scheduled naps including long naps early in the afternoon or short naps throughout the day
School accommodations [33]	Scheduled breaks for naps or during exams, shared notes from peers or teacher, extended time on exams and assignments, and excused absenteeism
Sleep hygiene [124]	Sleep-related behaviors to achieve appropriate hours of sleep
Sleep scheduling [3, 124]	Maintain a regular sleep schedule
Social support [124]	Resources and peer support communities from patient organizations
Work accommodations [33, 54]	Altered work schedule based on individual needs, additional training time, reassigning nonessential tasks to colleagues, special device/software/equipment accommodations, and disability leave

2.1 Cognitive Impairments

Narcolepsy has been associated with observed impairments in executive functioning, memory, attention, and decision-making [56, 57]. A cross-sectional survey of PWN in the USA demonstrated that cognitive difficulties were burdensome [36]. Of 1256 participants responding to the question, approximately half noted that difficulty thinking, remembering, concentrating, or paying attention was among the top three symptoms having most significant impact on their lives [36]. Mental fog/fogginess was also among the top three most impactful symptoms, reported by 20.6% and 30.7% of respondents with NT1 and NT2, respectively [36]. Pervasive brain fog, a chronic cognitive dysfunction that may possibly be linked to EDS, includes impaired attention and concentration, being in a daze, forgetfulness, lack of alertness, fatigue, and extreme confusion [58, 59]. No validated patient-reported outcome for brain fog is available despite common reports in narcolepsy and increasing public awareness owing to its association with long coronavirus disease 2019 (COVID-19) [59, 60]. Assessment or attempted treatment of brain fog, if performed, likely varies considerably among clinicians, making it difficult to determine if specific pharmacotherapies may ameliorate this distressing symptom.

Automatic behaviors, the performance of routine tasks without awareness, are commonly observed, affecting up to 40% of patients with narcolepsy [2]. Women with NT1 may be more likely to experience automatic behaviors compared with men with NT1 [41]. Reports of these automatic

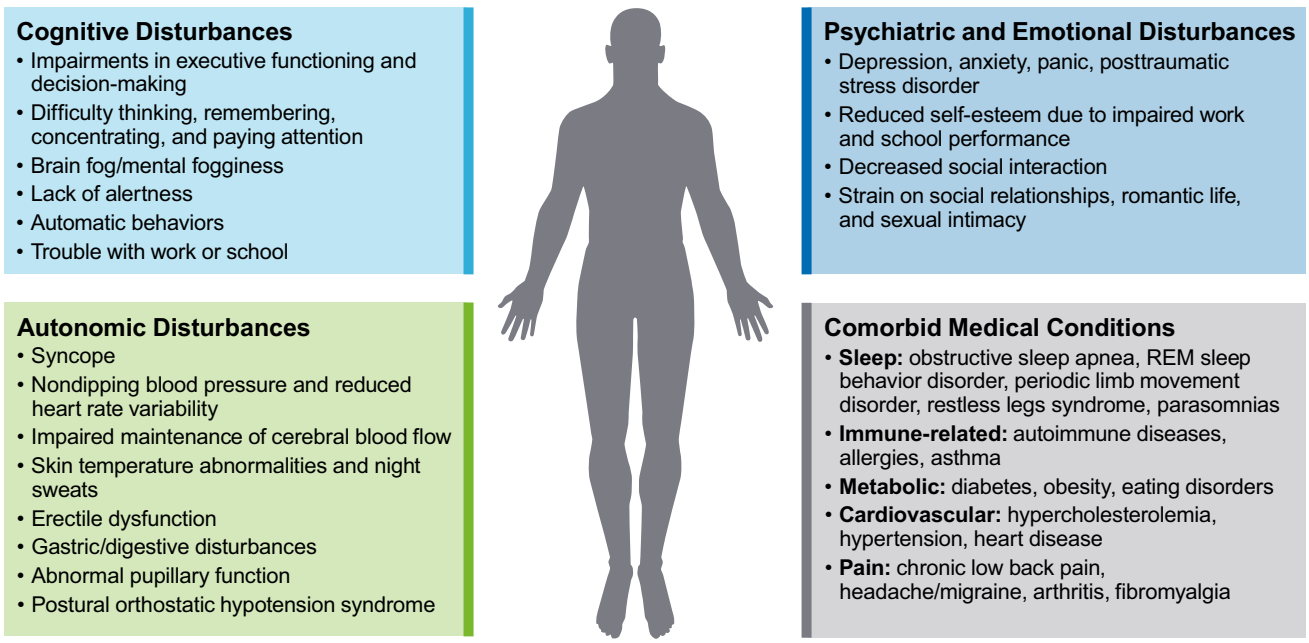

Fig. 1. Symptoms and features of narcolepsy beyond the classic pentad. *REM* rapid eye movement

activities have included cooking, putting items away, talking on the phone, writing or typing, and driving [2, 7]. Automatic behaviors have been associated with feelings of sleepiness, loss of recall, and activity errors leading to an unsuccessful task [7]. In a survey study, the majority of PWN reported being unable to perform at work or school and function in daily life as well as they would like, emphasizing the importance of considering these cognitive symptoms in a patient's care plan [36].

2.2 Psychiatric Disturbances

Narcolepsy has been associated with a greater prevalence of psychiatric disorders compared with the general population, including social anxiety disorder (21.1% versus 8.7%), major depressive disorder (17.1% versus 6.4%), panic disorder (12.5% versus 3.9%), and posttraumatic stress disorder (11.3% versus 5.3%) [61]. Other reports evaluating psychiatric and emotional disturbances in narcolepsy estimate the prevalence of depression and anxiety to be even higher (36–46% and 25–42%, respectively) [62, 63]. In a study of patients with NT1, women had significantly greater severity of depressive symptoms compared with men [41]. Approximately 25% and 35% of individuals with NT1 and NT2, respectively, have identified mood disturbance as one of the top three symptoms with most significant impact on their lives [36]. The overlapping symptomatology between narcolepsy and psychiatric disorders has led to diagnostic delays and challenges for many patients [64]. Depression, for example, is often a misdiagnosis prior to a narcolepsy diagnosis, in addition to being a common comorbidity [6].

It is unclear if these symptoms represent manifestations of the underlying neuropathology of narcolepsy, if they reflect a psychological response to the symptoms and psychosocial burden of the disease, or if they are better represented as an adjustment disorder with depressed mood [3, 65]. Narcolepsy has been associated with increased incidence of difficulties in work and school, as well as reduced self-esteem [3]. For some individuals, the debilitating condition has led to stigma, decreased social interaction, and strain on relationships with family, friends, or colleagues [58]. In a survey of 254 young adults with narcolepsy, the majority of respondents reported that the condition has led to more challenges in their social life (98%) and romantic relationships (88%), including sexual intimacy (81%) [66]. Results of cross-sectional and longitudinal analyses in adults with NT1 suggest that pharmacologic management of narcolepsy may improve depressive symptoms and suicidal thoughts [67]. In untreated patients who initiated pharmacotherapy, treatment was associated with improvements in depressive symptoms, EDS, and sleep-related outcomes; improvement in depressive symptoms correlated with improvement in narcolepsy symptoms [67]. Together, these findings underscore the importance of screening for depressive symptoms and suicidal thoughts in patients with narcolepsy and suggest that treatment for narcolepsy can substantially improve the psychological burden associated with this disease.

2.3 Autonomic Disturbances

Orexin-producing neurons are involved in autonomic nervous system pathways that regulate not only sleep-wake cycles but also energy metabolism, body temperature, and neuroendocrine and cardiovascular functions [68]. Autonomic disturbances reported in patients with NT1 included syncope, nondipping blood pressure (BP; defined as a $<10\%$ decrease in BP during sleep), reduced heart rate (HR) variability, erectile dysfunction, skin temperature abnormalities/night sweats, gastric or digestive disturbances, abnormal pupillary function, and impaired maintenance of cerebral blood flow during changes to BP or cerebral perfusion pressure [3, 69–76]. Compared with control subjects, patients with NT1 demonstrated significant impairments across gastrointestinal, urinary, cardiovascular, sexual, pupillomotor, and thermoregulatory subdomains in a study evaluating patient-reported autonomic symptoms [71]. Additionally, PWN have reported a form of autonomic dysfunction that manifests as very cold hands and feet [77].

Some patients may experience a specific type of autonomic disorder known as postural orthostatic hypotension syndrome (POTS), a chronic condition marked by increased daytime sleepiness, fatigue, and nighttime sleep disturbances, along with symptoms including dizziness, nausea, headache, shortness of breath, and difficulty thinking or concentrating. It is defined by excessive tachycardia when upright [an orthostatic HR increase of ≥ 30 beats per min (bpm); ≥ 40 bpm in individuals aged 12–19 years; or to ≥ 120 bpm] and improvement of symptoms upon recumbence [78–80]. Polysomnography (PSG) recording data demonstrating increased stage 2 sleep and reduced slow-wave sleep in patients with POTS, along with diminished patient-reported sleep quality, have further supported a link between autonomic dysfunction and sleep disruption [79]. POTS has been associated with decreased plasma volume, which should promote retention of sodium through the renin-aldosterone system; however, evidence suggests a deficiency in patients with POTS [78]. Administration of a high-sodium diet has been shown to increase plasma volume, decrease shifts in HR, and reduce standing plasma norepinephrine in patients with POTS relative to a low-sodium diet [78], and sodium supplementation is a mainstay of treatment for POTS [81].

2.4 Comorbid Medical Conditions

Compared with the general population, PWN have elevated rates of several medical comorbidities [61, 63, 82], which can have implications for the patient's treatment goals and care plan. A cross-sectional survey found that approximately two-thirds (67%, 973/1450) of individuals with narcolepsy must manage other diagnoses in addition to narcolepsy [36]. Overlapping symptoms between common comorbidities and narcolepsy can increase the complexity of diagnosis and medication management [3, 47].

2.4.1 Cardiovascular Disorders

In prior reports, higher prevalence of hypercholesterolemia, hypertension, and heart disease has been reported among PWN compared with the general population [adjusted odds ratio (AOR) range across conditions, 1.3–2.1; $P < 0.01$] [61]. However, in an analysis of electronic health record (EHR) data from a large, US-based healthcare system, cardiovascular-related comorbidities were found to affect PWN at similar rates compared with propensity-matched, non-narcolepsy controls (hyperlipidemia, 41% versus 43%; hypertension, 43% versus 42%; coronary artery disease, 8.4% versus 8.1%) [63]. It is unclear whether narcolepsy alone increases risk for cardiovascular disease (CVD). Further analysis of studies suggesting that CVD is increased in narcolepsy should ascertain other risk factors that may be more prevalent in PWN than in the general population, such as long-term use of amphetamine-based stimulants, obesity, and other lifestyle factors, such as diet and physical activity [83–86].

2.4.2 Autoimmune and Immunopathological Disorders

NT1 is hypothesized to be linked to an autoimmune pathogenesis [14, 87, 88], which could potentially lead to cooccurrence of additional immune-related conditions [89, 90]. In a longitudinal observational study of patients with NT1, comorbid autoimmune and immunopathological disorders were observed in nearly 30% (46/158) of patients, which is greater than the estimated rate in the general population [89]. Another study found that upper respiratory tract diseases, mainly allergies and asthma, were twice as frequent among PWN compared with the general population (AOR, 2.5; $P < 0.001$) [61].

2.4.3 Metabolic Disorders

Several studies have reported an association between narcolepsy and higher incidence of metabolic conditions, including diabetes and obesity, likely owing to the role orexin plays in regulation of food intake, body weight, energy expenditure, and lipid accumulation [91]. A retrospective analysis of US claims data found that PWN were more than twice as likely to be diagnosed with comorbid obesity relative to matched control groups [92]. A correlation between obesity and narcolepsy has been observed in both pediatric and adult patients [93]. Evidence has also linked narcolepsy to an increased likelihood of eating disorders, such as bulimia and binge eating [94]. Weight and body image concerns can potentially worsen psychiatric disturbances related to depression and anxiety, which as described earlier are common comorbidities for PWN [61].

2.4.4 Sleep Disorders

Obesity and increased weight have also been observed in patients with obstructive sleep apnea (OSA), which affects approximately 14.2% and 9.6% of individuals with narcolepsy with adult symptom onset and pediatric symptom onset, respectively; OSA is also a commonly reported misdiagnosis [6, 47]. Additional sleep-related comorbidities that are associated with a higher frequency in narcolepsy include REM sleep behavior disorder [RBD; versus controls, OR 44.0, 95% confidence interval (CI) 17.4–111.0], periodic limb movement (PLM) disorder (OR 14.8, 95% CI 12.0–18.1), and restless legs syndrome (RLS; OR 8.9, 95% CI 7.7–10.3) [92]. High rates of REM sleep without muscle atonia have also been reported in PWN irrespective of a diagnosed RBD comorbidity [95]. PWN often report parasomnias, such as vivid dreams, frightening nightmares, lucid dreams, and sleep walking [96].

2.4.5 Pain Disorders

Orexin deficiency has been implicated in pain, owing to several potential etiologies [97–99]. The findings that orexin neurons and receptors are localized in pain-processing brain regions, the observed analgesic effects of orexin in animal models of nociception, and the prohyperalgesic activity of orexin A receptor antagonists under inflammatory conditions support the role of orexin in nociception [97–99]. High incidence rates of pain-related comorbidities have been reported among patients with narcolepsy, including chronic low-back pain, headache/migraine, and arthritis [92, 100, 101], along with higher frequency of self-reported pain compared with controls [97]. Presence of a migraine diagnosis in children has been associated with a higher risk and cumulative incidence of narcolepsy compared to children without migraine [102]. Additionally, fibromyalgia was identified as a common comorbidity (7.4%) in a cross-sectional survey of individuals with narcolepsy in the USA [36]. Further, in a cohort study using EHR data, pain-related disorders (chronic pain syndrome, migraine, fibromyalgia, carpal tunnel syndrome, myalgia) represented 5 of the top 20 comorbidities occurring

more frequently in patients with narcolepsy compared with propensity-matched controls [63].

2.5 Safety Considerations for Pharmacologic Management

In patients requiring multiple medications to treat narcolepsy symptoms, potential drug–disease interactions with medical comorbidities should be considered. Concerns have been previously raised about the high sodium content of SXB treatment for narcolepsy with respect to BP and cardiovascular risk [84]. However, during its extensive history of use as a treatment for narcolepsy in clinical practice and trials, SXB has not been associated with changes in BP or increased risk of adverse cardiovascular outcomes [103, 104]. Most antidepressants[46] can cause weight gain, whereas solriamfetol and SXB can cause weight loss [46, 105–108]. SXB can cause central nervous system (CNS) depression, which has potential to exacerbate OSA; before prescribing SXB, the presence of moderate or severe OSA should be determined, and sleep apnea should be treated [46, 109]. Given the risk of CNS depression with oxybates, caution should be used when prescribed with other CNS depressants; concomitant use of alcohol and/or sedative hypnotics is contraindicated [49, 50, 109]. Patients with a history of depression or suicidal ideation should be monitored while receiving an oxybate. Clinicians and patients should also be aware of the risk for parasomnias, including sleepwalking, with the use of oxybates and ensure proper safety precautions are in place. Oxybates are only available through risk evaluation and mitigation strategy programs through the FDA to ensure safe use of these medications. Stimulants, including mixed amphetamine salts and methylphenidate, have a high potential for abuse or misuse; therefore, clinicians must evaluate each patient's risk before prescribing [110, 111]. Additionally, caution with stimulant use should be applied in patients with preexisting cardiovascular conditions, as increased heart rate and blood pressure have been linked to stimulant use and may elevate the risk of adverse cardiac outcomes [112, 113]. Solriamfetol may also increase blood pressure and heart rate, and clinicians should periodically assess and monitor these parameters [114]. Patients with known QT prolongation should avoid the use of pitolisant, as it can increase the QT interval [115]. Serious reactions, such as Stevens–Johnson Syndrome, angioedema, and multiorgan hypersensitivity, have been reported in patients taking modafinil and armodafinil, along with psychiatric adverse reactions, including depression, anxiety, and agitation [116, 117]. Clinicians should be aware of the broader symptoms and features of narcolepsy when developing a comprehensive care plan, playing close attention to subsets of patients with special considerations, such as those with multiple comorbidities requiring complex medication regimens.

3 Additional Considerations Across the Patient's Lifetime

As is generally the case with management of a chronic disease, considerations for management and treatment selection may differ over time based on the patient's age, lifestyle, and comorbidities (Fig. 2) [47].

3.1 Pediatric Patients

Given the peak onset of symptoms in adolescence (approximately 15 years) [34], narcolepsy may be viewed as a pediatric onset disease. In children and adolescents, screening, early diagnosis, and prompt initiation of therapy are essential to minimize the emotional and developmental impact of narcolepsy, including reduced educational achievement [47]. Differences in narcolepsy presentation have been reported between pediatric and adult patients, and diagnosis of pediatric narcolepsy may be delayed owing to a variety of reasons, including lack of symptom recognition and a need for better education and awareness of this rare disorder among pediatricians [6, 30, 118].

EDS is often the first symptom in pediatric narcolepsy but may often be overlooked as apathy or normal napping behavior by caregivers. It may present as other behaviors, such as irritability, hyperactivity, inattentiveness, aggression, social withdrawal, or shyness, masking EDS and further delaying proper diagnosis [30, 118]. EDS in adolescents with narcolepsy may also be mistaken for developmental and puberty-related changes in sleepiness, sleep habits, and circadian rhythms [119]. In children, sudden sleep attacks may last longer compared with those observed in adults, and tiredness may return within a few hours of napping [30, 118]. Additional EDS symptoms observed in pediatric narcolepsy include sleep "drunkenness," which is an extreme difficulty in arousing children in the morning that may accompany combativeness, confusion, and even difficulty with coordination [30].

Cataplexy has been reported to present in approximately 56–95% of pediatric narcolepsy cases [120, 121]. Features of cataplexy in pediatric patients with narcolepsy may be either active or negative motor phenomena and may occur with or without emotional triggers [122, 123]. In contrast with adults, pediatric cataplexy may involve active motor phenomena, which are hyperkinetic movements, such as facial grimacing, spontaneous tongue protrusion, tic-like movements, and automatic behaviors of self-scratching and touching [9, 30, 118, 122, 124]. Negative features of pediatric cataplexy are transient losses of muscle tone, including head drop and falls, facial/eyelid weakness, and slurred speech [9, 30, 122, 124]. Additional complex behaviors can include neck extension viewing and puppet-like movements [9].

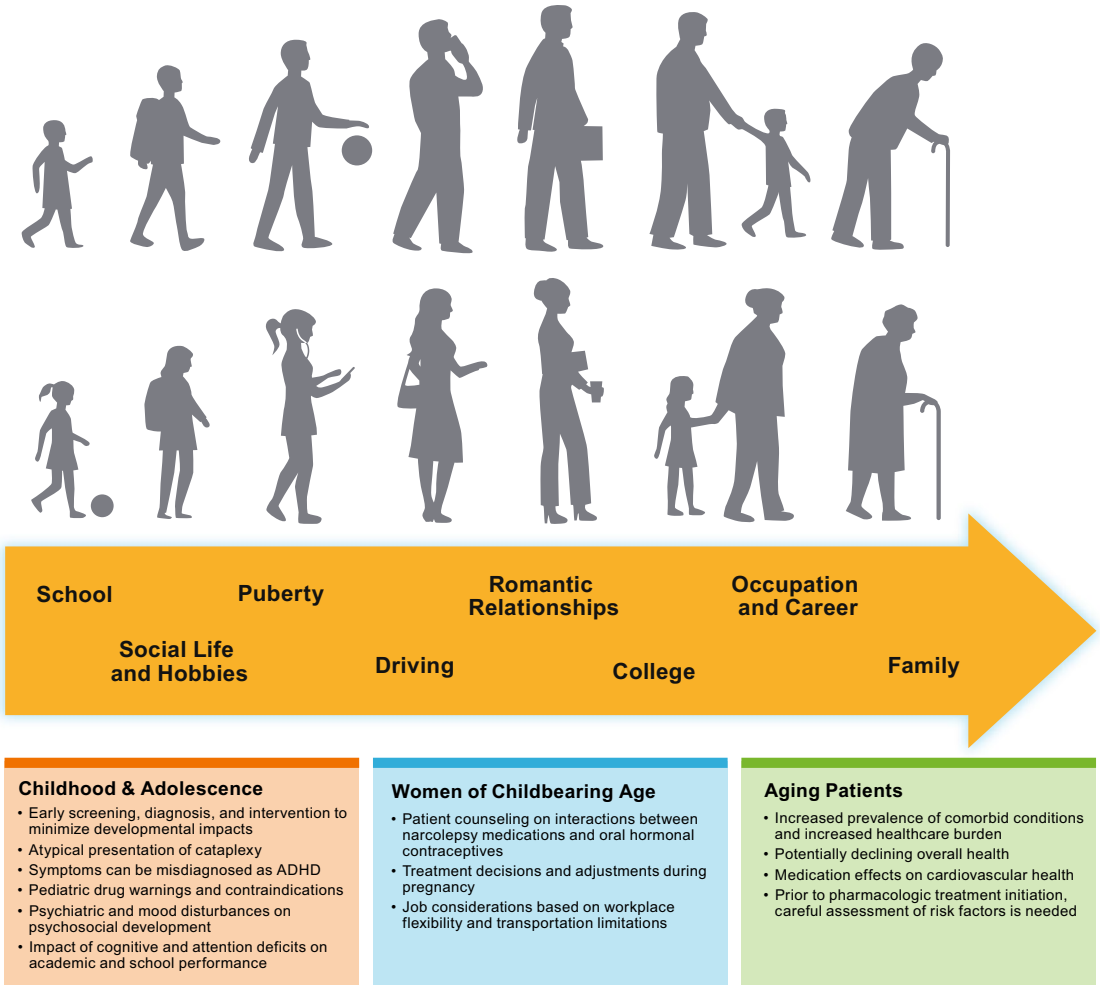

Fig. 2. Treatment considerations for narcolepsy across the life span. *ADHD* attention-deficit/hyperactivity disorder

These features can coexist [125] and may be misperceived as clumsiness, seizure activity, or attention-seeking behavior [118]. Pediatric narcolepsy also shares typical features observed in adults, including sleep paralysis, hypnagogic/hypnopompic hallucinations, and DNS, along with increased PLM and RBD [30, 118].

Sudden onset of weight gain in early childhood has been observed in pediatric patients with narcolepsy, and obesity is a common comorbidity in these patients [126, 127]. Findings have shown that pediatric patients with rapid weight gain were younger, sleepier, and more obese at narcolepsy diagnosis than those without rapid weight gain, suggesting a more severe and accelerated disease phenotype [128]. Additionally, pediatric narcolepsy has been linked to early onset of puberty, with literature reporting a high prevalence of precocious puberty prevalence among children with narcolepsy involving cataplexy [126]. While a precise mechanism has not been established, it has been theorized that orexin acts as an inhibitory agent in the release of gonadotropin-releasing hormone (GnRH); thus, deficiency of orexin in children with NT1 may lead to early GnRH activation and puberty onset [129]. Notably, younger age at narcolepsy symptom onset has been recognized as a predictor of precocious puberty and childhood obesity [126].

Cognitive/attentional impairments can affect school performance, socialization, self-esteem, and mood. An online survey of 116 parents of children aged ≤22 years with narcolepsy and 35 pediatric (aged 12–22 years) patients with narcolepsy found that the most frequent and problematic symptoms associated with narcolepsy in the pediatric population were EDS, DNS, and depression/mood challenges [127]. Difficulty focusing/memory problems, schoolwork, worry about the future, getting easily upset, and diet/nutrition were identified as the most frequently rated psychosocial challenges both by parents and youth with narcolepsy, highlighting the adverse impact of cognitive symptoms [127]. Anxiety and depression were among the most common comorbidities in pediatric patients [127]. Impaired school performance, along with related cognitive symptoms (hyperactivity, impulsivity, difficulty maintaining attention),

in pediatric narcolepsy result in overlapping clinical presentation with attention-deficit/hyperactivity disorder (ADHD), a common comorbid condition [30, 118, 130]. Deficits in academic performance and attention/concentration, along with behavioral issues, may be mistaken for substance abuse in some older children [131].

The AASM guidelines conditionally recommend modafinil for treatment of EDS and SXB for treatment of EDS, cataplexy, and disease severity in pediatric populations [48]. In children, the EU guidelines recommend first-line treatment with methylphenidate, modafinil, SXB, amphetamine derivatives, or pitolisant monotherapy for EDS only/predominant and SXB monotherapy or combination therapy for patients with EDS and cataplexy with or without DNS [4]. With the exception of SXB in the USA and methylphenidate in some EU countries, these recommendations are based on off-label usage [4, 48]; the European Medicines Agency authorized a pediatric indication (≥ 6 years of age) for pitolisant in March 2023 [132], subsequent to publication of the EU guidelines.

Certain drug warnings and contraindications are particularly relevant with respect to pediatric pharmacotherapy. Methylphenidate and amphetamines in children/adolescents can induce psychotic-like symptoms, especially at high doses [133]. In children, long-term treatment with stimulants, such as methylphenidate and amphetamines, can suppress growth [5, 134]. Additionally, while rare in clinical practice, severe rashes, including Stevens–Johnson Syndrome, may be more likely to occur in children than adults during treatment with modafinil/armodafinil [47, 135, 136].

3.2 Women of Childbearing Age

In a survey of women of childbearing age with narcolepsy, > 40% of respondents reported that they did not receive adequate counseling from their narcolepsy physician regarding pregnancy and contraception [137], suggesting there is opportunity for increased patient education. An important consideration when treating women of childbearing age is that some medications induce cytochrome P450 enzymes and may thereby reduce the effectiveness of steroidal contraceptives [135, 136]. Notably, less than one-fourth of survey respondents received information about interactions between narcolepsy treatments and contraceptives from their providers [137]. When oral hormonal contraceptives are used concomitantly with pitolisant and modafinil/armodafinil, dosage adjustment of the contraceptive should be considered and use of alternative methods of contraception is recommended through 1 month after discontinuation of pharmacotherapy [4, 45, 47]. As there have been no clinically significant interactions reported [4, 45, 50], SXB and solriamfetol may be suitable treatment options for these patients as there is no requirement for a secondary form of contraception owing to a decreased risk of drug–drug interactions relative to other wake-promoting agents.

During pregnancy, reduced severity of NT1 symptoms, including cataplexy, has been observed for some women [4]. Decisions regarding whether to continue with possible dose reduction, switch, or withhold pharmacologic treatment of narcolepsy during pregnancy should be made in collaboration with an informed patient after considering the risks and benefits [47]. Approximately one-third of women with narcolepsy reporting pregnancies discontinued pharmacologic treatment of narcolepsy during pregnancy; the most common reasons included personal fear of harm to the fetus and advisement from physicians [137]. There is little evidence of clinically significant teratogenicity with therapeutic doses of SXB, methylphenidate, and amphetamines [138], and results of ongoing pregnancy registries may provide additional guidance [115, 139]. A systematic review of available data, including from the Swedish Birth Registry among other sources, found that the prevalence of congenital malformations among infants exposed to methylphenidate during the first trimester was not higher than expected [140]. An analysis of data from the US Provigil/Nuvigil Pregnancy Registry identified a potential increased risk of major congenital malformations following in utero exposure to modafinil/armodafinil relative to the general population (13/102 live births; 13% versus 3% in the general population); however, no specific organ malformation pattern or clear causal association was identified [139]. For patients with severe symptoms that merit continuing pharmacotherapy, consultation with maternal-fetal medicine specialists may be helpful. Hormonal fluctuations during pregnancy may affect the sleep cycle and may be beneficial, as subjective improvements in sleep have been observed in postmenopausal women receiving estrogen [141, 142]. Nonpharmacologic management strategies used by patients during pregnancy include extended sleep time, increased caffeine intake, discontinuation of work and/or driving, and increased napping [137]. Social support and pregnancy education resources are available from patient organizations such as Wake Up Narcolepsy, Hypersomnia Foundation, and Project Sleep.

3.3 Aging

Many comorbid medical conditions, along with presence of multimorbidity, become more prevalent with increasing age [143]. Older adults in the general population notably have higher prevalence rates of various CVDs, including hypertension, heart failure, stroke, and coronary heart disease, and CVD-related mortality compared with younger adults [144]. Prior to pharmacologic treatment initiation, careful assessment of risk factors, including those related to cognitive, cardiovascular, and organ function, should be conducted

in older patients, who often have reduced quality of life, greater healthcare burden, and higher mortality risk relative to the general population. Certain antidepressants should be avoided in older patients owing to risks associated with sedating effects and orthostatic hypotension [145]. Additionally, methylphenidate and amphetamines should be used with caution in patients with CVD or glaucoma and may be suboptimal choices in many older adults with narcolepsy [47]. Limited data are available on the specific use of SXB in older adults. A retrospective study evaluating long-term use of SXB for narcolepsy with cataplexy in routine clinical practice found no differences in the efficacy of SXB on daytime sleepiness and cataplexy frequency on the basis of age [146]. However, age was associated with an increased risk of psychosis and enuresis [146]. Older patients taking SXB should be assessed for adverse reactions, with consideration of discontinuation if these increase to a concerning degree. All patients should be counseled to take their dose of SXB while in bed and lie down immediately after administration [49, 50, 147]; this is particularly important for older patients, owing to the increased risk of falls with advanced age [148]. Some clinical characteristics, including renal or hepatic impairment and concomitant medications, may impact drug clearance or metabolism, which could pose safety risks and require dose adjustments or use of alternative medications in older adults with narcolepsy [149]. Comprehensive care management for this lifelong condition should consider the patient's age, overall health, and potential challenges associated with pharmacotherapy.

4 Conclusions

Narcolepsy is a chronic, lifelong disease with no cure. Care considerations for narcolepsy should extend beyond the classic pentad to include other clinically relevant or concerning symptoms that include cognitive, psychiatric, and autonomic disturbances. An individualized treatment approach is recommended and should incorporate addressment of the most concerning symptoms and patient goals, as well as age and stage of life, comorbid conditions, and overall health. An interdisciplinary approach should be considered when clinical needs are represented by multiple specialties. Ongoing reevaluation of treatment goals and strategy are required over time owing to evolving needs and expectations over the lifetime of an individual with a chronic neurologic disorder.

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