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REVIEW ARTICLE

Sodium Oxybate: Practical Considerations and Patient Perspectives

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Abstract
Narcolepsy is a rare, chronic sleep disorder with significant impacts on the quality of life of people affected by the disorder. People with narcolepsy (PWN) are a diverse patient population with evolving symptoms, comorbidities, and perspectives. As PWN have varying needs, clinicians should consider a more personalized approach to therapy, including active participation of PWN in their care and shared decision-making between patient and clinician to achieve optimal outcomes. In this review, we discuss the various characteristics and challenges of PWN, present illustrative clinical case scenarios of PWN, provide clinicians with a proposed framework to best address therapy for PWN, and demystify concerns with sodium oxybate.

Key Points

People with narcolepsy (PWN) are a diverse population with varying symptoms that evolve over time.

Clinicians have an important role in empowering PWN to be active participants in their care.

1 Introduction

Narcolepsy is a rare, chronic sleep disorder that confers significant daily burdens on the lives of people affected by the disorder [1]. Symptoms of narcolepsy, which include excessive daytime sleepiness (EDS), cataplexy, and disrupted nighttime sleep (DNS), have a significant negative impact on the quality of life of people with narcolepsy (PWN) [1, 2]. PWN often face challenges and delays in receiving a diagnosis, likely due to narcolepsy being rare [1], a lack of symptom recognition by clinicians [3], diverse symptomatology [2], and often acceptance of their suboptimal, ongoing symptoms. As PWN present with varying symptom profiles, goals for therapy, and lifestyle factors, clinicians should include the patient in the development of a personalized treatment plan [2]. In this review, we explore the diverse perspectives of PWN and how patients and clinicians can share in therapy decision-making to achieve optimal outcomes. We present two illustrative case report scenarios of PWN that clinicians may encounter to provide practical insights and guidance for effective management in a clinical setting.

2 Diverse Needs Among PWN

PWN are a diverse patient population comprising multiple clinical phenotypes [4]. The age of narcolepsy symptom onset peaks in adolescence [5–7]. However, many individuals do not receive a clinical diagnosis for years after symptom onset, owing to lack of symptom recognition and misdiagnosis [8]. Data from the Unite Narcolepsy survey demonstrated diagnostic delays ranging from 1 to > 10 years after onset of symptoms [9]. Approximately 82% (1193/1451) of responders were not diagnosed with narcolepsy until a year or more after symptom onset, and approximately 32% (436/1350) did not receive a diagnosis for > 10 years after symptom onset [9]. Similarly, a survey of members of the MyNarcolepsyTeam social network showed that 31% (34/110) of respondents did not receive a

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diagnosis of narcolepsy for ≥ 10 years [10]. Furthermore, diagnosis in the pediatric population presents an additional challenge, as presenting symptoms may be nonspecific and different from the adult population, such as behavioral or mood disturbances and excessive sleeping [6].

Illustrative Patient Case Scenario: Ryan

Ryan is an 18-year-old man who will be starting his first year of college in 2 months. When Ryan was 12 years old, he was diagnosed with attention deficit/hyperactivity disorder (ADHD) by his pediatrician and initiated immediate-release (IR) mixed amphetamine salts twice daily. Shortly thereafter, his family and teachers observed a marked change in his behavior; he was no longer fidgety in class or putting his head down on his desk. He seemed to have returned to his normal self.

However, 2 years later, Ryan began to have difficulty sleeping. He could fall asleep quickly, but he never felt as though his sleep was refreshing. Even worse, Ryan began to dread going to bed, as he had terrifying nightmares of someone coming into his room at night; he described this as feeling "like being in a movie."

Multiple comorbidities, including other sleep disorders, weight gain and obesity, depression, anxiety, and behavioral problems, have been linked with narcolepsy [1], which can confound a clear diagnosis [2]. Evidence suggests that disordered eating, such as night-eating syndrome and binge eating behavior, may also be associated with narcolepsy [11, 12]. Additionally, medications prescribed for PWN may further exacerbate sleep-related eating disorder (SRED), a parasomnia characterized by somnambulism and compulsive eating with impaired recall [13, 14]. In a disproportionality analysis of medication-associated SRED ($N = 676$), cases were most commonly associated with zolpidem (36%) and IR sodium oxybate (27%) [13]. SRED events with IR sodium oxybate may coincide with the second nightly dose [14]. Psychosis and schizophrenia have been rarely reported in PWN; an analysis of the Slovakian Narcolepsy Database described three cases of patients with narcolepsy type 1 (NT1) and psychosis, concluding that those with NT1 diagnosed at age ≤ 18 years may have a higher risk of psychotic disorders owing to higher vulnerability during the ongoing neurodevelopmental period [15]. As patients seek a diagnosis, they may visit a number of specialists, such as a psychiatrist, a rheumatologist, or a functional medicine provider, prior to receiving a referral to a sleep specialist. Results from a survey of physicians ($n = 400$) showed that 62% of sleep specialists and only 24% of primary care physicians were "very" or "extremely" knowledgeable about narcolepsy [3]. MyNarcolepsyTeam members were also surveyed to determine whether they had received an initial diagnosis of something other than narcolepsy [10]. Of the 110 responders, 64% did not receive an initial diagnosis of narcolepsy. The most common initial diagnoses among respondents were depression (73%), sleep apnea (36%), insomnia (19%), or ADHD (16%). Thus, greater awareness of the symptoms of narcolepsy is needed among all medical specialties. An emphasis on narcolepsy symptom recognition from primary care providers is warranted, as they are often the first clinician a patient may turn to when seeking a solution for their symptoms.

Illustrative Patient Case Scenario: Holly

Holly is a 39-year-old woman who works as an accountant at a fast-paced accounting firm. When she was in her 20s, she often felt sleepy throughout the day. This profound sleepiness significantly lowered her work performance, and she quickly fell behind her peers. The few times she attempted to discuss her sleepiness with her primary care provider, she was told that these feelings were normal and simply a result of her demanding job and raising two young children. Despite not feeling any symptoms of depression, she was prescribed fluoxetine, which she found had no effect on her daytime sleepiness.

Years later, Holly experienced a near-miss accident while driving to the grocery store with her children. She felt a sudden onset of sleepiness at a red light and was awakened by the sound of a car horn blaring after the light had long turned green. At this moment, Holly realized that there may be more underlying her extreme sleepiness than just a busy schedule.

3 Prioritizing Patient Perspectives and Shared Decision-Making

Shared decision-making is an approach to patient care in which input from both the clinician and the patient is considered to empower patients to make informed treatment decisions [16]. When patients are well informed, they may develop more realistic expectations of treatment, as they understand the benefits and risks of each option [16]. In the context of narcolepsy, shared decision-making aims to treat the main symptoms of narcolepsy and prioritize the patient's most bothersome symptoms, while accounting for lifestyle factors, comorbidities, and concomitant medications [17]. Active participation of the patient in treatment decisions may enhance treatment adherence as well [2]. In a meta-analysis of 53 studies evaluating the effect of patient preferences on psychotherapy treatment outcomes and dropouts, patients who were given their preferred treatment had better outcomes compared with patients who were assigned a psychotherapy ($P < 0.001$), and patients who were not provided with their preferred treatment were more likely to

discontinue therapy compared with patients who were given a choice in their treatment ($P < 0.001$) [18]. Furthermore, a systematic review of 115 articles evaluating patient preferences in treatment decision-making found that, in 63% of analyses, respondents preferred to participate in treatment decisions with their clinician [19]. Results of this review also indicate an increasing preference of patients to participate in treatment decision-making in recent years.

Illustrative Patient Case Scenario Continued: Holly

Holly shares the story of her near-miss incident with her clinician and is then referred to you, a sleep specialist. At her initial visit, she explains that her sleepiness has affected more than just driving; her work performance has slipped as well. For the last 4 months, she has experienced daily feelings of an irrepressible need to sleep. She has been caught nodding off in meetings with her manager and constantly feels a brain "fog." Furthermore, her relationship with her husband is suffering, as her sleepiness prevents her from doing the activities they used to enjoy together, such as cooking family dinners, going on date nights, or even watching TV together. She currently takes an oral steroid contraceptive and sodium tablets for postural tachycardia syndrome (POTS), which she was diagnosed with at the age of 35 years. Initially, Holly thought that the POTS diagnosis was the reason for her sleepiness. Although the sodium tablets have helped with the syncope she would sometimes experience, nothing else has changed.

Holly agrees to complete an overnight sleep study followed by a multiple sleep latency test (MSLT). Her mean sleep latency is 6 minutes, and during the MSLT, three sleep onset rapid eye movement periods (SOREMPs) occurred. There is no evidence of obstructive sleep apnea on her sleep study. Given her Epworth Sleepiness Scale (ESS) score of 18 and the results of the MSLT, you diagnose her with narcolepsy type 2 (NT2).

To effectively develop a treatment plan and empower patients in their treatment decisions, clinicians must strive to form positive and trusting relationships with their patients. A greater sense of trust between patient and clinician is built when clinicians collect a complete medical history and gain an understanding of the patient's personal goals and preferences for therapy [20]. These interactions provide a point of reference for future visits. Also, many patients are educated about their condition and may come to visits with therapy ideas in mind. Thus, clinicians should stay up-to-date on therapies and trends in sleep medicine to adequately address patient concerns and questions.

It is important for patients to have appointments throughout the diagnostic and treatment phases, with ongoing appointments thereafter to continue open discussions regarding progression of their disorder and treatment effectiveness. As patients return for follow-up visits, multiple topics should be discussed. Points for discussion at these visits may include primary symptoms, comorbidities, medications, and goals or expectations for therapy. Special attention should be given to concomitant medications that may worsen narcolepsy symptoms, as well as potential drug–drug interactions (Table 1) [17]. To evaluate the efficacy of treatments, clinicians should also consider asking patients what they are able to do now that they were not able to do at the previous visit, and remind them of their initial chief complaint and ESS score before they received treatment. These types of questions may help demonstrate to patients the progress they have made in what is specifically meaningful to them. This helps to realign the patient's perspective on the efficacy of their treatment and guide the clinician to the next priority the patient would like to address. A checklist (Fig. 1) for follow-up appointments may be beneficial in guiding discussions.

Illustrative Patient Case Scenario Continued: Ryan

After sharing his symptoms with his pediatrician, Ryan was referred to you, a sleep specialist, for further evaluation. Upon interview, you learn that he had recently stopped playing baseball, a game he loved, because he would suddenly become clumsy during practice or games. Ryan had previously been a star player but had missed several big catches owing to the ball slipping out of his hands. His mother added that he had recently gained weight but was not sure whether it was puberty or stopping sports. Ryan felt as though his ADHD was mostly under control, but he would sometimes find himself nodding off while riding in the car. Given Ryan's symptoms (sleepiness despite treatment with mixed amphetamine salts, DNS, hypnagogic hallucinations, cataplexy, and recent weight gain) and ESS score of 15, you order a sleep test. An overnight polysomnography reveals no evidence of sleep-disordered breathing, but does show numerous sleep stage shifts, nocturnal arousals, a rapid eye movement latency of 3 min, and 1 SOREMP, while the next-day MSLT shows a mean sleep latency of 2 min. You share with Ryan and his family that he has narcolepsy with cataplexy, also called NT1.

The International Classification of Sleep Disorders, Third Edition, Text Revision guidelines for NT1 diagnosis now include one nocturnal polysomnogram SOREMP, defined as rapid eye movement sleep within 15 min of sleep onset, as a standalone criterion, revised from previous diagnostic criteria that only allowed it to substitute one of two required SOREMPs on a MSLT [21]. Historically, narcolepsy treatments have focused on daytime

Table 1 Potential narcolepsy drug–drug interactions

Drug	Interaction
Dopaminergic drugs	Caution with use with solriamfetol [76]
Drugs that increase blood pressure or heart rate	Caution with use with solriamfetol [76]
Drugs that cause CNS depression[a]	Consider dose reduction or discontinuation of oxybates or other CNS depressants [54, 55, 59]
H1 receptor antagonists[b]	Avoid concomitant use with pitolisant [75]
Monoamine oxidase inhibitors	Avoid concomitant use with solriamfetol, methylphenidate, or mixed amphetamine salts [76, 78, 79]
QT-prolonging medications[c]	Avoid concomitant use with pitolisant [75]
Sedative hypnotics or alcohol	Contraindicated with oxybates [54, 59]
Serotonergic drugs	Caution with use with methylphenidate and mixed amphetamine salts [78, 79]
Steroidal contraceptives	Decreased contraceptive efficacy if used with modafinil, armodafinil, or pitolisant; use nonhormonal contraceptive [75, 80, 81]
Substrates of CYP2C19	Increased systemic exposure if used with modafinil [81]
Strong CYP2D6 inhibitors[d]	Decrease pitolisant dosage by half if used concomitantly; caution with use of mixed amphetamine salts [75, 79]
Strong CYP3A4 inducers[e]	Assess for loss of efficacy with pitolisant if a CYP3A4 inducer is initiated; decrease pitolisant dosage by half if a CYP3A4 inducer discontinued [75]

CNS central nervous system

[a]Benzodiazepines, general anesthetics, muscle relaxants, and opioid analgesics; sedating antidepressants, antiepileptics, or antipsychotics

[b]Diphenhydramine and tricyclic antidepressants

[c]Class 1A antiarrhythmics, disopyramide, procainamide, and quinidine; Class 3 antiarrhythmics, amiodarone, and sotalol; antipsychotics and ziprasidone

[d]Bupropion, fluoxetine, and paroxetine

[e]Carbamazepine, phenytoin, and rifampin

symptoms [22]; however, of the five symptoms of the narcolepsy symptom pentad (i.e., EDS, cataplexy, DNS, sleep paralysis, and hypnagogic or hypnopompic hallucinations), three are mostly nocturnal in nature [1, 23]. Given that narcolepsy is characterized by an inability to regulate the sleep–wake cycle, consideration of the 24-h impact is critical [4]. Approximately two-thirds of PWN are estimated to have nocturnal sleep disturbances [24]; however, one survey showed that only 45% of respondents' clinicians discussed nighttime sleep with them, with 43% of clinicians discussing therapies for nighttime sleep [10].

As the narcolepsy treatment path is often nonlinear, clinicians should set expectations with patients from the beginning of their treatment journey. For many PWN, more than one medication may be needed; each medication may address different aspects of the narcolepsy pentad through its unique mechanism of action, and when used concomitantly, PWN can have better resolution of their symptoms [25]. While some medications begin working relatively quickly, other medications may take several weeks to show efficacy [26, 27]. Clinicians should always review potential side effects with PWN and help them understand which side effects are common and which are rare, that side effects may dissipate over time and/or be dose dependent, and when to contact the office. After "setting the stage" with expectations for therapy, clinicians can give patients time to think about their treatment options and return with an informed decision (Table 2).

4 Empowering Patients to Take an Active Role in Narcolepsy Management

Encouraging patients to take an active role in their care can be difficult, as patients may not always be forthcoming with their treatment challenges, or they may provide inadequate or incomplete responses in an attempt to please their clinician. A survey evaluating the types of information most commonly withheld from clinicians was administered to two participant groups: one group ≥ 18 years of age and one group ≥ 50 years of age [28]. Approximately 81% of the ≥ 18 years age group and 61% of the ≥ 50 years age group reported that they had withheld medical information from a clinician. The most common reasons for nondisclosure of medical information were to avoid being judged or lectured, being told that the behavior is harmful, being embarrassed, being labeled a "difficult patient," and taking too much of the clinician's time. Some patients may have concerns that their treatment will be taken away if they are completely honest about their symptoms. Similarly,

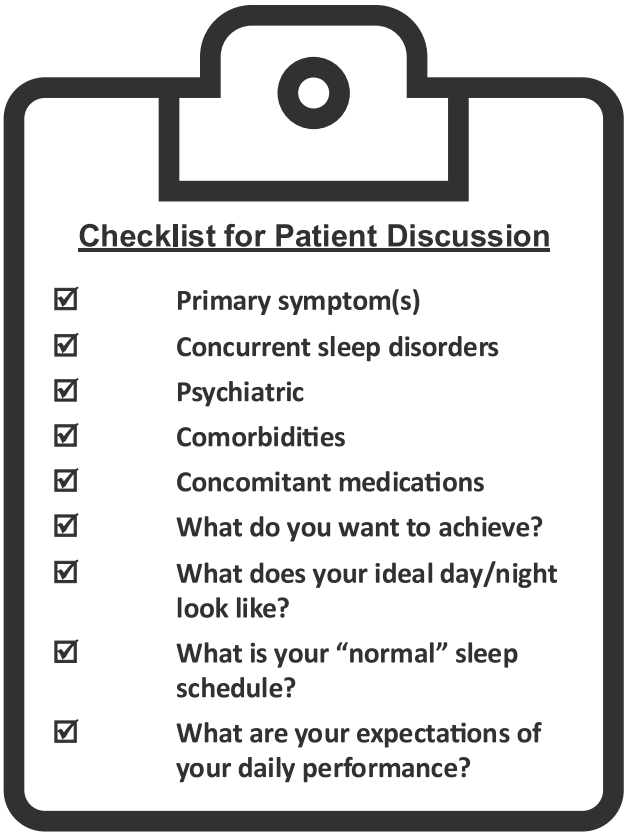

Fig. 1 Checklist for patient discussion. Adapted from Morse et al. Presented at World Sleep 2022; March 15, 2022 [85]

patients may not know what to share and may require more direct questions from the clinician during their visits. Specifically, hallucinations may not be disclosed, as patients may fear being judged or being labeled by others. Patients may also not volunteer symptoms that frighten them [29]. Thus, it is paramount that patients acknowledge the purpose and importance of keeping open lines of communication with their clinician. Patients may not be adequately treated if the provider does not have a clear picture of what patients are experiencing [30].

Illustrative Patient Case Scenario Continued: Holly

You explain to Holly that you would like to start her on a new medication, modafinil, to treat her NT2 and ask her to return in 1 month to monitor her progress. You also explain that modafinil may reduce the effectiveness of her oral steroid contraceptive.

When Holly returns for her follow-up appointment, she relays that she is thrilled with how modafinil has improved her daytime wakefulness. She feels as though she is a completely different person at work. However, you administer the ESS and find a score of 14. Furthermore, she describes using most of her energy at work and struggles to fully engage with her family when she returns home. She reports "tossing and turning" at night when trying to sleep and inquires if she may have insomnia as well. Holly denies experiencing hallucinations, but when you describe sleep paralysis to her, she is surprised to learn that the "weird thing" she has been experiencing on and off since her 20s has a name. You let Holly know that many PWN require more than one medication to adequately control all their symptoms and that you can add a medication to her regimen today if she feels ready. Holly states that she wishes to wait a few months longer before changing her regimen, so you schedule a follow-up with her in 3 months.

As PWN may face stigma from family members and peers due to a lack of understanding, opportunities for PWN to connect with each other and advocacy organizations may offer a sense of empowerment and validation [29]. Results of a questionnaire fielded to participants of online support groups demonstrated that, by participating in the group, members felt more informed regarding their illness and had an improved sense of social well-being [31]. Participation in support groups may also foster improved dialogue between patient and clinician, as ≥ 50% of questionnaire respondents shared that they felt more prepared for their appointments, could clarify their needs better, and knew which questions to ask. Patient advocacy organizations such as Narcolepsy Network, Wake Up Narcolepsy, and Project Sleep offer resources for PWN and their families to connect with other PWN, access educational resources, and increase awareness of the disorder [32–34]. Understanding coping strategies and their impact on quality of life can help clinicians develop tailored interventions to reduce maladaptive behaviors, such as disengagement and denial, which are associated with lower quality of life [35]. PWN may benefit from interventions that promote more effective, adaptive coping techniques, such as active coping and seeking support [35].

Illustrative Patient Case Scenario Continued: Ryan

Ryan's family respond to the diagnosis with skepticism and worry that he will not lead a productive life; their only knowledge of narcolepsy is from the movie "Deuce Bigelow." You spend time with the family to help them understand that narcolepsy is a neurologic disorder in which the brain cannot regulate the sleep–wake cycle, and it affects about 1 in 2000 people. You assure Ryan and his family that you will be present throughout his entire treatment journey to create a plan incorporating both pharmacologic and nonpharmacologic treatments.

Given Ryan's symptoms of cataplexy, DNS, and EDS, you discuss initiating IR sodium oxybate; you explain that the medication requires two nightly doses and

Table 2 Comparison of available oxybate formulations

	Xyrem® (sodium oxybate) [54]	Xywav® (calcium, magnesium, potassium, and sodium oxybates) [55]	LUMRYZ™ (sodium oxybate) [59, 82]
Active drug moiety	GHB		
Contraindications	Alcohol Sedative hypnotics SSADH deficiency[a]		
Dosing	1 dose administered at bedtime and another dose administered 2.5–4 h later, at least 2 h after eating		1 dose administered at bedtime, at least 2 h after eating
Administration	1. Prepare both doses by extracting the prescribed amount from the 180 mL multi-dose bottle with the dosing syringe (medicine will not flow into the syringe unless the bottle is kept upright) 2. Each dose should be mixed with 60 mL of water prior to consuming		1. Fill the mixing cup to line A with water 2. Open the pre-measured dosing packet and pour in the contents 3. With the lid on, shake for 60 seconds and consume 4. Fill the cup to Line B, shake for 10 seconds, and consume[b]
Additional considerations	Counsel patients to reduce dietary sources of sodium (fast food, packaged/processed foods), as the 9 g dose contains 1640 mg of sodium	Contains sucralose, an artificial sweetener Contains calcium, magnesium, and potassium	Counsel patients to reduce dietary sources of sodium (fast food, packaged/processed foods), as the 9 seconds g dose contains 1640 mg of sodium
Setting patient expectations	• Common side effects are nausea, headache, vomiting, bedwetting, and anxiety • Most side effects lessen as patients become accustomed to a dose • Proactively discuss enuresis management • Patients may notice improved sleep in the first few weeks, but may not experience full efficacy in the first few weeks • Advise patients that the first few weeks on an oxybate may be the most challenging, as this tends to be when side effects are most likely, but full efficacy has not yet been achieved		

GHB γ-hydroxybutyrate, *SSADH* succinic semialdehyde dehydrogenase

[a]SSADH deficiency is a rare disorder in which patients are unable to metabolize GHB [83]

[b]Product specification experiments demonstrate that approximately 97–100% of the dose is delivered after shaking the mixing cup for just 10 s [84]

could help with Ryan's nighttime sleep disturbances. The family expresses confusion regarding the need for a second dose in the middle of the night, but you explain that, because the medication is short acting, the first dose must be taken at bedtime and the second dose 2.5–4 h later. Ryan's parents agree to take turns waking up at night to administer Ryan's medication. You also change Ryan's twice-daily IR mixed amphetamine salts to a once-daily extended-release (ER) formulation of mixed amphetamine salts.

Ryan starts your prescribed regimen: IR sodium oxybate 2.25 g twice nightly for 2 weeks, followed by 3.0 g twice nightly for 2 weeks, 3.75 g twice nightly for 2 weeks, and then 4.5 g twice nightly. At his 1-month follow-up visit, Ryan describes feeling groggy in the morning with some difficulty initiating and staying asleep. As a result, you increase Ryan's bedtime dose and lower his second dose.

When you check back 1 month later, Ryan's symptoms are better controlled; by 2 months, he is even playing baseball again. Despite his improvement, it has been a hardship for his parents, both of whom work, to wake up to give him the second dose. Ryan describes feeling guilty for making his parents wake up in the middle of the night, every night. However, he was unable to consistently wake up for the second dose when he tried on his own.

5 Evolving Symptoms and Patient Priorities

Narcolepsy symptoms may evolve throughout a patient's lifetime; thus, clinicians must recognize and anticipate these changes to address them promptly. PWN have reported assessing severity of their disorder by functional capacity and impairment rather than frequency or severity of symptoms, which may differ from the clinician's assessment approach [36]. Anticipated and internalized stigma toward symptoms is common, adding to the psychological distress PWN may experience [36].

After starting treatment, PWN may initially feel much better than they did at baseline. However, other symptoms of narcolepsy that were once masked by symptoms that are now treated may become more prominent and merit dosing adjustments or polypharmacy. In clinical trials of various oxybate formulations, individuals taking alerting agents (approximately 60–90% of the overall population) still had pathologic sleepiness to qualify for inclusion in the trial [37–41]. Although a majority of the Unite Narcolepsy survey respondents did not report any changes to their symptom profile since diagnosis, approximately 22% (304/1373) had "worse and more unpredictable" symptoms, and approximately 6% (81/1373) reported feeling "more overwhelmed and less prepared to manage narcolepsy symptoms" [9]. Data from a survey of > 1000 PWN showed that approximately 83 and 84% of respondents with NT1 and NT2, respectively, could not perform as they wished at work or school owing to their diagnosis [9]. Furthermore, approximately 63 and 33% of respondents with NT1 and NT2, respectively, could not drive a vehicle without limitations. People with NT1 have demonstrated deficits in alertness, short and sustained attention, and increased error rates [42, 43]. Therefore, clinicians play an important role in recognizing symptoms and adjusting treatment plans accordingly.

Illustrative Patient Case Scenario Continued: Holly

Holly reaches out to you 3 months later. She feels as though the effect from modafinil has plateaued. She is starting to feel as though she could nod off during a meeting again. She continues to have arguments with her husband regarding her sleepiness as well. You ask Holly to make an appointment and request that her husband attend the visit with her.

At this visit, you let them know that narcolepsy can be a challenge for relationships; many people do not fully understand that narcolepsy is a neurologic disorder. You educate both Holly and her husband that this diagnosis is by no fault of Holly.

You explain that Holly's difficulty sleeping at night is called DNS, and approximately two out of three PWN experience it. You review additional treatment options with Holly and her husband and explain that many medications taken during the day will address daytime sleepiness but not DNS.

Family attendance at follow-up visits can be helpful, as they provide additional insight and perspective to a patient's symptom profile. These visits also serve as an opportunity for families to learn more about their loved one's diagnosis and the best ways to support them. For pediatric PWN, school teachers may further inform narcolepsy treatment response [2].

Sometimes, patients may not realize that the symptoms they are experiencing are abnormal. Many symptoms may be difficult to verbalize, such as the relationship between cataplexy and strong emotions, particularly for children [29]. Parents may also not recognize certain behaviors of their children as symptoms of narcolepsy. Thus, clinicians should be able to describe these symptoms to patients using descriptions and/or examples that are readily understood (Table 3).

Illustrative Patient Case Scenario Continued: Ryan

Four years later, Ryan and his mother return for a routine, semi-annual follow-up appointment. Since initiating IR sodium oxybate 4 years ago, Ryan's par-

Table 3 Verbiage to help patients understand narcolepsy symptoms

Narcolepsy symptom	Patient verbiage
EDS	Do you get sleepy during the day and have the urge to take a nap or fall asleep inappropriately? Do you get a burning sensation in your eyes or have a difficult time keeping your eyes open? How alert do you feel during the day? Do you have a hard time waking and getting moving in the morning? Are you able to complete the work, personal, and family tasks that you aim to achieve? What are you able to accomplish after receiving treatment for narcolepsy that you were not able to accomplish before?
Cataplexy	During the day, do you have any abrupt onset of weakness, tingling, or numbness on your body? Do you ever feel as though you are holding onto something, but then it feels as though it flies out of your hand? Has one side of your face ever felt heavy, or has your head ever bobbed forward on its own, unrelated to poor sleep quality or lack of sleep? If yes, do any of these things ever happen when you feel heightened emotion, such as anger, surprise, laughter, or excitement?
DNS	Do you wake up often, even if for a very brief or extended amount of time? Has your bed partner ever told you that you were a restless sleeper? Do you feel as though your sleep at night is satisfying? Do you feel rested the next day after sleeping?
Hypnagogic/hypnopompic hallucinations	When you are awake, going to sleep, or asleep trying to wake up, what we call the sleep transition period, do you see or hear your dreams as if it is reality? If you are dreaming, for example, of a train, do you physically see or hear the train next to you? Do you feel as though you are dreaming but not actually asleep? Do you have a difficult time realizing whether you are in real life or dreaming—and it may be because of something you see, hear, or feel? Do you see scary or frightening things in your room (e.g., shadows, images)?
Sleep paralysis	Have you ever been asleep, then wake up, know you are awake, and even feel your eyes looking around the room, but you can't move your body?

DNS disrupted nighttime sleep, *EDS* excessive daytime sleepiness

ents have woken up every night to administer his second dose. For a brief period when Ryan was 16 years old, he wanted to use his own alarm clock to wake up and take his second dose. However, the alarm clock woke up his younger sister more consistently than himself. As a result, Ryan's parents resumed taking turns administering the second nightly dose.

As Ryan is graduating from high school and beginning college soon, he is adamant that he will live on his own in a dorm room. Ryan's parents express concerns that he will not be able to wake up on his own to take his second dose or that he may be placed in a dorm with untrustworthy roommates.

Upon hearing these concerns, you offer to write a letter of accommodation to the university, advocating for Ryan to have a single room. While the parents appreciate this offer, they still worry that Ryan will not be capable of taking his second dose while living alone. Ryan's mother offers to call him each night to wake him up, but Ryan wants to feel independent as he starts this new stage of his adult life. He also does not want to begin school while being isolated in a single room.

You acknowledge and validate their concerns and review all available treatment options. Then, you discuss with Ryan and his mother a new ER, once-nightly formulation of sodium oxybate that is now available. This medication is released throughout the sleep period, resulting in low levels in the morning.

Ryan and his mother are thrilled to learn that there is an option that does not require waking up in the middle of the night or leaving out a second dose of medication unattended in a dorm room.

6 Demystifying Sodium Oxybate: Practical Considerations for Patient Success

Sodium oxybate was first studied as treatment for narcolepsy nearly 50 years ago [44] but did not gain US Food and Drug Administration (FDA) approval until 2002 [45] and European Medicines Agency (EMA) approval until 2005 [46]. Despite sodium oxybate being recognized as a standard of care and strongly recommended by the American Academy of Sleep Medicine for more than 15 years [47, 48], sodium oxybate remains underutilized [49], which may be due to lack of education for both clinicians and PWN.

Sodium oxybate has a well-characterized safety profile; when taken at therapeutic doses (6–9 g per night), adverse events are primarily issues of tolerability, which are generally mild to moderate and transient [38–40, 50–53]. Educating patients on the timing of side effects is important, as

most will be felt at initiation and with dose increases and will diminish with time [38, 52]. Many clinicians inform patients that the full therapeutic effect of sodium oxybate may not be felt for several weeks after initiation. Counseling patients on the risk of central nervous system (CNS) depression is critical, as CNS depressants, such as sedative hypnotics or alcohol, are contraindicated with the use of sodium oxybate [47, 54, 55]. Sedative hypnotics, such as zolpidem, are sometimes prescribed for PWN owing to the common nature of nocturnal sleep disturbances [56, 57]; however, these medications do not treat daytime symptoms of narcolepsy [58] as sodium oxybate does [24, 47]. Counseling of PWN to help them understand the need to transition from sedative hypnotics to sodium oxybate is warranted. Anxiety is a recognized adverse event with oxybates [38, 40, 52]; unlike other adverse events, anxiety may not always ameliorate over time. It is hypothesized that the anxiety experienced by some patients may be related to being more connected or present in daily life; patients may be more aware of daily stressors after their EDS symptoms markedly improve following treatment with an oxybate. Psychosocial support in the form of peer narcolepsy groups and/or therapy may be useful not only for anxiety but also for living with a chronic and typically "invisible" disorder. In addition, it may be helpful to consider decreasing doses of alerting agents, which may exacerbate anxiety, or consider the addition of a selective serotonin reuptake inhibitor.

Sodium oxybate is the sodium salt of γ-hydroxybutyrate (GHB) [59]. For some patients and clinicians, an unfortunate stigma remains for GHB, as illicit use of the drug has been implicated in sexual assault [60]. Owing to the risk of abuse, misuse, diversion, or central nervous system depression, the FDA requires a Risk Evaluation and Mitigation Strategies (REMS) program for all oxybate medications [61, 62]. The REMS has stringent oversight of the prescribing and dispensing of oxybate medications and extensive counseling for patients to help ensure appropriate use and safety. To ensure the safe and effective use, the EMA similarly requires a Risk Management Plan (RMP) for twice-nightly sodium oxybate to identify, characterize, and minimize risks [63, 64]. The RMP consists of a controlled distribution system and patient educational materials [63, 65].

Illustrative Patient Case Scenario Continued: Holly

You ask Holly and her husband whether they have heard of the oxybate class of medications. Holly states that she is a member of a Facebook group for PWN and has seen many members describe the benefits of the medication. However, she has reservations about the drug considering its history as a "date rape drug," and questions how a drug taken at night will help with daytime sleepiness.

You explain that sodium oxybate has been approved by the FDA for more than 20 years and requires a strict safety program. You provide additional reading materials about sodium oxybate and ask them to return in 2 weeks after they have taken time to consider the medication as an option.

When Holly returns, she expresses more interest in sodium oxybate. You explain that there are three different formulations available. Two of the three options are IR and require one dose to be taken at bedtime and a second dose 2.5–4 h later. The third formulation is an ER version of sodium oxybate and requires just one dose at bedtime. Holly cannot imagine waking up her husband with an alarm each night to take the dose or leaving the second dose at her bedside. She agrees to try once-nightly sodium oxybate (ON-SXB), as a once-nightly formulation sounds far more appealing than a twice-nightly formulation. You counsel Holly on the most common side effects patients experience with ON-SXB, including nausea, vomiting, headache, dizziness, and bedwetting, and let her know that these are generally transient and most frequently experienced when first starting the medication and at dose increases. You also discontinue the sodium tablets that Holly had been taking for POTS owing to the additional sodium in ON-SXB.

Holly returns for a follow-up in 2 months. Her ESS score has improved to 11, and she reports sleeping soundly at night; even her husband's sleep has improved as she is no longer "tossing and turning." Holly states that, since starting ON-SXB, she is able to spend more quality time with her family, her relationship with her husband has significantly improved, and she is more productive at work.

Sodium oxybate is a highly effective medication; however, PWN may find dose timing and preparation challenging [66]. Twice-nightly oxybates require administration of the first dose at bedtime and then waking 2.5–4 h later to administer the second dose [54, 55]. RESTORE was a long-term, open-label study to evaluate the safety and tolerability of ON-SXB and the ability to switch from a twice-nightly oxybate to ON-SXB [67]. In the RESTORE study, 64.6% (84/130) of participants who were receiving twice-nightly oxybate prior to the start of the study had unintentionally missed the second dose of their medication in the 3 months prior to study initiation [67]. Of the participants who unintentionally or intentionally missed their second dose of twice-nightly oxybates, 80.2% (73/91) felt worse the next day. These data demonstrate some of the challenges PWN face when using twice-nightly oxybates.

Some clinicians may reserve sodium oxybate only for people with NT1; however, both individuals with NT1 and

with NT2 may benefit from the medication [68]. American and European narcolepsy treatment guidelines place a strong recommendation on sodium oxybate for the treatment of narcolepsy based on demonstrated clinical efficacy for EDS or cataplexy [24, 47].

DNS can occur in patients with either NT1 or NT2 [5]. While PWN generally fall asleep relatively quickly [69], they often experience highly fragmented sleep, including recurrent awakenings or frequent sleep stage shifts that may contribute to patient complaints of nonrestorative sleep, despite having a normal amount of total sleep time [70]. Evaluations of sleep parameters with IR sodium oxybate must take the twice-nightly dosing regimen into consideration, as some assessments, such as total sleep time, need to be conducted during the "first half" and "second half" of the night [71, 72]. As demonstrated by Black et al. [72], slow-wave sleep was increased during the second half of the night with the 9-g dose of IR sodium oxybate compared with the first half of the night. These results contradict normal sleep architecture, wherein slow-wave sleep usually occurs earlier in the nocturnal sleep period [73]. Early peak concentrations observed with ON-SXB are theorized to correspond with more slow-wave sleep in the first part of the night, aligning with a more normal sleep architecture [74]. Subjective measures of sleep, such as sleep quality and the refreshing nature of sleep, are also important considerations in assessing treatment efficacy. An analysis of DNS parameters from the REST-ON trial showed significant improvement from baseline in patient-reported sleep quality and refreshing nature of sleep compared with placebo at all tested doses ($P < 0.001$) [41].

Illustrative Patient Case Scenario Continued: Ryan

Ryan raises concerns that his symptoms have been controlled on IR sodium oxybate for many years, and he is fearful of making a change in his current regimen. His mother also has concerns that 7.5 g of sodium oxybate in a single dose could be dangerous. You validate Ryan's concerns by acknowledging that change can be scary; however, to achieve his goal of becoming more independent, starting ON-SXB may be worthwhile. To address his mother's concerns, you show both Ryan and his mother a graph of how IR sodium oxybate and ON-SXB release medication over time, explaining that both medications release the same amount of medication, but ON-SXB releases some of the medication later in the night and further down the gastrointestinal tract compared with the IR formulation. You suggest starting the medication during the summer when he is at home with his family so that he can acclimate to the medication prior to starting college. Both Ryan and his mother feel reassured and decide to make the switch to ON-SXB.

As ON-SXB requires a different method of preparation, you counsel both Ryan and his mother on how to reconstitute and administer the medication. You explain that each dose comes in a premeasured packet; each night before bed, Ryan is to fill the provided container with water to the marked line, empty the packet into the container, shake for 60 seconds, drink the contents, and then rinse the container with more water and drink the contents. You let him know that, unlike his prior medication, this is a suspension, meaning there will be particles floating in the water that do not dissolve.

Ryan and his mother return in 1 month for a follow-up visit. Ryan reports that the dosing regimen of ON-SXB has greatly simplified his life. His mother adds that the whole family is thankful to no longer be chronically awakened each night to administer a second dose of IR sodium oxybate. Ryan is confident that he will be able to manage his new medication at college and is looking forward to the independence this will bring.

Patients may have reservations prior to starting an oxybate. Some PWN fear that they will not be rousable to emergency situations at night after taking a dose of sodium oxybate. Clinicians can advise patients to request a friend or spouse to wake them at night after initiating sodium oxybate should an emergency situation develop. PWN may choose to initiate the medication when they have more time off from work (i.e., teachers during the summer). In addition, many patients are referred to sleep specialists while receiving multiple medications, such as stimulants, benzodiazepines, or sedative hypnotics. Patients may fear that these medications will be discontinued if they initiate sodium oxybate. Clinicians should explain to patients that both sedative hypnotics and oxybates may increase the risk of CNS depression; therefore, if an oxybate is taken, sedative hypnotics will need to be discontinued [54, 55, 59]. In addition, dosage reductions of benzodiazepines or oxybates may be required if used concomitantly. If a patient develops anxiety after initiating SXB, a discussion of potentially lowering the alerting agent dose should occur. Some patients may need encouragement from their clinician to recognize that naps can help them feel more refreshed, as well as support from their workplace to accommodate this need. However, if naps are increasingly needed, this may be a signal to consider adjusting the dose of a medication or adding a medication with a different mechanism of action. Assuring the patient of your partnership to find the appropriate regimen will make them feel supported during this time.

7 Conclusions

PWN are a diverse patient population with various needs and comorbidities. Clinicians should work with their patients to prioritize their perspectives and tailor treatment plans to their symptoms, comorbidities, lifestyle factors, and concomitant medications. Checklists may be used as a framework to promote open dialogue between clinician and patient and can encourage patients to take an active role in managing their narcolepsy. As narcolepsy symptoms evolve over a patient's life, one may not fully understand or may be hesitant to ask about the treatment options available to them. Clinicians must ask the right questions and recognize when treatment changes are necessary.

The expanded options of FDA-approved medications for narcolepsy allow patients and clinicians to individualize therapy to meet specific patient needs throughout their lifetime. The last decade has brought the narcolepsy community four additional FDA-approved treatments [55, 59, 75, 76]. A new class of medications, orexin agonists, has progressed beyond animal studies and into phase 2 and phase 3 trials [77].

Oxybate medications are an important component of the current treatment armamentarium and can now be utilized as a single, extended-release bedtime dose. All oxybate medications necessitate close collaboration between the patient, their loved ones, and their healthcare team to achieve optimal patient goals.

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