

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column gave informed consent for the publication of the column. A bibliography for this column is available in the online version at [jpn.ca](http://jpn.ca).*

## Missed diagnosis of long-standing narcolepsy

Craig Chepke, MD

A 31-year-old man presented to the outpatient psychiatric clinic seeking treatment for previously diagnosed attention-deficit/hyperactivity disorder (ADHD) and depression. He received the ADHD diagnosis at the age of 9 years and the depression diagnosis as a teenager. He found little symptom relief despite treatment; medications were routinely switched throughout his youth. At first visit, medications included amphetamine-dextroamphetamine salts (10 mg, twice daily) and fluoxetine (40 mg/d). Previous medications included escitalopram, vortioxetine, venlafaxine, extended-release amphetamine-dextroamphetamine salts, methylphenidate, lisdexamfetamine and atomoxetine, with little clinical benefit.

When the patient described the effect of stimulants on concentration as lasting only briefly, the interviewer asked questions about excessive daytime sleepiness. The patient described experiencing excessive daytime sleepiness since childhood, and feeling sleepiness “beyond belief,” with only brief relief from stimulants. Further, his mind always felt foggy, as if in a dream state. He sometimes had to hold his eyelids open while driving. He was asked if he ever felt his knees get weak in response to emotional stimuli. He explained that, recently, a dog behind him barked and he fell onto the ground. He ultimately described experiencing cataplexy frequently enough to be bothersome. He also endorsed having hypnagogic and hypnopompic hallucinations.

The patient’s medical history included ADHD, depression and suicidal ideation. He had no diagnosed family history of sleep disorders.

The patient was referred to a sleep specialist for polysomnography and a multiple sleep latency test to confirm a suspected diagnosis of narcolepsy type 1. His sleep study showed a total sleep time of 353.2 minutes, no clinically significant sleep-disordered breathing or other sleep disturbance, a mean sleep latency of 2 minutes and 21 seconds and 0 sleep-onset rapid eye movement (REM) periods. This was consistent with, but not classic for, narcolepsy because of the absence of sleep-onset REM periods.<sup>1</sup> Upon diagnosis of narcolepsy type 1 (without any comorbidities), the psychiatrist prescribed armodafinil 250 mg/d. After 4 weeks, the patient was seen for follow-up with his psychiatrist. Calcium, magnesium, potassium and sodium oxybate (i.e., low-sodium oxybate, marketed as *Xywav*) was added to his regimen (2.25 g, twice nightly for 1 wk, to be titrated to 3.75 g, twice nightly).<sup>2</sup> Low-sodium oxybate is a central nervous system depressant approved by the US Food and Drug Administration for treatment of cataplexy or excessive daytime sleepiness in patients aged 7 years or older with narcolepsy and for treatment of idiopathic hypersomnia in adults.<sup>2-5</sup> Low-sodium oxybate is also approved by Health Canada for treatment of cataplexy in adult patients with narcolepsy (aged  $\geq 18$  yr) with narcolepsy. The mechanism of action of low-sodium oxybate is not well understood, but it is proposed to involve  $\gamma$ -aminobutyric acid-B actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.<sup>2</sup>

At diagnosis, the patient’s Epworth Sleepiness Scale (ESS) score was 22. After 6 weeks of armodafinil and low-sodium oxybate, he returned to the psychiatrist with marked clinical improvement (ESS = 7). He reported that low-sodium oxybate changed his life. Within a few weeks, he stopped

napping, he had no excessive daytime sleepiness, and his concentration, work performance and family relationship improved. He did not self-report or give the impression of experiencing anxiety or depression, and reported no cataplexy, even in startling events. Therefore, his psychiatrist stopped the armodafinil. After 12 weeks, he returned feeling well, but reported some excessive daytime sleepiness since stopping armodafinil (ESS = 12). The psychiatrist increased his low-sodium oxybate (4.5 g, twice nightly); solriamfetol (75 mg/d) was added 2 weeks later. At his final follow-up, he denied excessive daytime sleepiness and wished to continue the current regimen. He reported that his father and sister, who had similar symptoms but were diagnosed and treated for mood disorders and ADHD, subsequently received diagnoses of narcolepsy and responded well to low-sodium oxybate.

Narcolepsy is an uncommon central hypersomnolence disorder with 2 subtypes.<sup>6</sup> Narcolepsy is characterized by symptoms of excessive daytime sleepiness, cataplexy (in narcolepsy type 1 only), disrupted nocturnal sleep, hypnagogic or hypnopompic hallucinations, and sleep paralysis.<sup>6,7</sup> Further, psychiatric comorbidities such as anxiety and depression are common.<sup>8</sup> Early narcolepsy diagnosis may improve patient care and outcomes, and helps avoid unnecessary or ineffective treatments.<sup>9,10</sup>

Narcolepsy is often misdiagnosed because symptoms may mimic those of other neuropsychiatric disorders, delaying diagnosis and treatment.<sup>8,9,11</sup> Psychiatric clinicians should consider narcolepsy, particularly in patients reporting excessive daytime sleepiness and uncontrolled depression or ADHD.<sup>10</sup> Key probing questions may relate to excessive daytime sleepiness (e.g., “Even if you do not have the

opportunity, how badly do you want to take a nap during the day?”, “Do you drink caffeinated drinks to keep from feeling sleepy?”), cataplexy (e.g., “Do you ever feel like your muscles get weak if you are startled or feel some other emotion?”), hypnagogic or hypnopompic hallucinations (e.g., “Do you feel like part of a dream intrudes into the real world and you see something that is not actually there right after you wake up or right before you fall asleep?”) and sleep paralysis (e.g., “Do you ever feel like your brain and body wake up at different times, such that you feel you cannot move right after you wake up or right before you fall asleep?”). For this patient, the relationship between the psychiatrist and sleep specialist allowed for efficient identification of narcolepsy and treatment optimization with low-sodium oxybate. This relationship between providers ensures accurate and timely diagnosis and treatment. Psychiatric clinicians’ awareness of narcolepsy symptoms and use of key probing questions can improve disease outcomes with tremendous impact on quality of life for patients and, potentially, their families.

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**Competing interests:** Craig Chepke has served on the advisory boards of AbbVie, Acadia, Alkermes, Axsome, Biogen, Eisai, Idorsia, Intracellular, Janssen, Jazz, Karuna,

Lundbeck, Moderna, Neurocrine, Otsuka, Sage, Takeda and Teva; served as a consultant for AbbVie, Acadia, Alkermes, Axsome, Biogen, Corium, Eisai, Intracellular, Janssen, Jazz, Karuna, Lundbeck, MedinCell, Neurocrine, Otsuka, Sage, Sunovion and Teva; has received grant or research support from Acadia, Axsome, Harmony, Neurocrine and Teva; and has been on the speaker’s bureau for AbbVie, Acadia, Alkermes, Axsome, Eisai, Genomind, Intracellular, Janssen, Jazz, Lundbeck, Merck, Neurocrine, Otsuka, Sunovion and Teva. No other competing interests were declared.

**Funding:** This article was supported by Jazz Pharmaceuticals, which manufactures Xywav. Under the direction of the author, Shawn Jaramillo and Sean Anderson of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support, which was funded by Jazz Pharmaceuticals.

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**Cite as:** *J Psychiatry Neurosci* 2023 December 20;48(6). doi: 10.1503/jpn.230097

## References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition, Text Revision (ICSD-3-TR)*. Darien, IL: American Academy of Sleep Medicine; 2023.
2. Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2023.
3. Szarfman A, Kuchenberg T, Soreth J, et al. Declaring the sodium content of drug products. *N Engl J Med* 1995;333:1291.
4. *Quantitative labeling of sodium, potassium, and phosphorus for human over-the-counter and prescription drug products. Guidance for industry*. Silver Spring, MD: US Food and Drug Administration; 2022. Available: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug> (accessed 2022 Oct. 11).
5. *Clinical review for Binosto, NDA 202344*. Silver Spring, MD: US Food and Drug Administration; 2012. Available: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202344Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf) (accessed 2023 Feb. 28).
6. Barateau L, Pizza F, Plazzi G, et al. Narcolepsy. *J Sleep Res* 2022;31:e13631.
7. American Academy of Sleep Medicine. Narcolepsy type 1. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
8. Morse AM, Sanjeev K. Narcolepsy and psychiatric disorders: comorbidities or shared pathophysiology? *Med Sci (Basel)* 2018;6:16.
9. Dunne L, Patel P, Maschauer EL, et al. Misdiagnosis of narcolepsy. *Sleep Breath* 2016;20:1277-84.
10. Ruoff CM, Reaven NL, Funk SE, et al. High rates of psychiatric comorbidity in narcolepsy: findings from the Burden Of Narcolepsy Disease (BOND) study of 9,312 patients in the United States. *J Clin Psychiatry* 2017;78:171-6.
11. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med* 2014;15:502-7.