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LETTERS TO THE EDITOR

The Treatment of Narcolepsy With Amphetamine-Based Stimulant Medications: A Call for Better Understanding

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It is possible for a clinician not specializing in sleep medicine to work an entire career and never come across a patient with narcolepsy. In the United States narcolepsy has an incidence of approximately 1:2,000 individuals,[1] which according to the 2010 census yields approximately 154,350 Americans with the disorder. Narcolepsy is then considered a rare disease according to the Rare Diseases Act of 2002, which defines as rare any disease affecting fewer than 200,000 Americans.

Given that rarity and the fact that the disorder is not well understood even by a significant number of sleep medicine clinicians,[2] the unintentional withholding of adequate treatment from patients with narcolepsy is a common occurrence. In this letter the disorder will be discussed first, and then practical clinical considerations will be outlined.

The neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively), are produced in a small population of neurons in the lateral hypothalamus.[3] Initially identified in 1998, the orexins were originally understood to be regulators of feeding behavior and energy storage and expenditure.[4,5] Soon it became clear that the orexins also play a substantial role in the regulation of sleep/wake states[6] and that the loss of orexinergic signaling (regardless of the cause, which was yet unknown) causes narcolepsy.[7,8] Later work painted a much larger picture: taking inputs from internal and external sensors, orexin neurons formulate and execute appropriate responses to changing conditions through regulating or modulating emotion,[9,10] the reward response,[10–13] homeostasis,[14] cognition and executive function, thermogenesis, olfactory function, intestinal motility, reproductive drive, motivated behaviors, and many other functions of the autonomic nervous system.[15] Excitatory orexin neurons quickly direct other proteins, neurotransmitters, hormones, and various other neurochemicals to perform their functions.

The four main symptoms of narcolepsy are excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnopompic/hypnagogic hallucinations. Experienced sleep medicine clinicians understand that not all patients with narcolepsy experience all symptoms and that the manner in which any patient with narcolepsy experiences his or her symptoms changes over time.[16] They also understand that the loss of orexinergic signaling that is the cause of those symptoms is also the cause of the dysregulation of other autonomic functions, as mentioned previously.[17] A primary care provider faced with a patient with narcolepsy (diagnosed or otherwise) presenting with an odd assortment of apparently unrelated symptoms, unsure of a reason for or even of the validity of the patient's claims, would not be faulted for making a diagnosis of "dysautonomia." Strictly speaking, that is what it may well be, but it is likely that what they have been looking at is all part of the "package" that includes narcolepsy.

We feel that the broad range of pathologies resulting from lost orexinergic signaling, both directly and as a result of cascading failures of dependent systems, and including the specific group of symptoms called narcolepsy, should fall under a single all-inclusive disorder that we propose to name "Hypocretin/Orexin Signaling Disorder," or "HOSiD."

One of the most bothersome and disabling symptoms of narcolepsy is EDS. There are several ways of treating EDS. Of those, one of the more common is to prescribe amphetamine-based stimulants. In a 2007 article by the Standards of Practice Committee of the American Academy of Sleep Medicine appearing in the journal *Sleep*, the authors state, "amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy."[18]

The literature contains considerable research demonstrating that the administration of an orexin receptor antagonist to an individual addicted to alcohol or cocaine completely or substantially extinguishes the reward response and therefore the craving for the drug.[19–22] Having few or no orexin neurons, the brains of people with narcolepsy produce this same result. To the best of our knowledge, no formal studies have been done to conclusively determine or even document the fact that people with narcolepsy are inherently resistant to drug addiction, although there are passing mentions of this in the literature. For example, in their 2013 article entitled "The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine functions," Inutsuka and Yamanaka say, "…psychostimulants such as amphetamine or methylphenidate are often given to narcolepsy patients. Interestingly, drug addiction hardly occurs in these patients. This finding suggests that the orexin system mediates the establishment of drug addiction."

Regarding amphetamine-based stimulants, the authors of the aforementioned article in *Sleep*[18] state, "These medications

have a long history of effective use in clinical practice but have limited information available on benefit-to-risk ratio. This lack of information may reflect the limited sources of research funding for medications available in generic form rather than clinical utility of these medications."

With that last statement, the authors go right to the heart of the matter. The sensitivity of the subject, especially now, in the shadow of the current epidemic of opiate use, makes it unlikely that any public funder of research will fund a study that aims to show that any group of people are resistant to drug addiction. Yet because there has not been even casual research into the question of whether there is drug addiction in narcolepsy, many people with narcolepsy are caused undue suffering.

Unaware as they are that people with narcolepsy rarely become addicted to these drugs and conditioned to think of them as dangerous, many physicians hold back from prescribing them. They would rather write prescriptions for nootropic drugs for wakefulness or potentially dangerous but widely used hypnotic drugs for better sleep before resorting, for example, to Adderall, Dexedrine, Vyvanse, or Desoxyn to combat EDS. When they do prescribe amphetamines, physicians often prescribe doses that are too small to manage the sleepiness of narcolepsy.

Very often a patient with narcolepsy needs several months or even 1 year of experimenting with various doses of various drugs before finding the drug and the dose that works for them, a situation that repeatedly brings them back to the clinician to request a change in dosage. An experienced sleep clinician knows that although a small number of people with narcolepsy will have bad reactions to this class of drugs, most can take doses of amphetamines that would kill otherwise healthy people within minutes, washing them down with mug of strong coffee, and then going back to sleep. However, when people with narcolepsy are treated by physicians who are unaware of their resistance to addiction, their patients' pleas for larger doses are often seen as drug seeking and their requests are denied. We often hear of physicians telling their patients with narcolepsy the well-intentioned fiction that they are at the maximum legal dose and they cannot prescribe anything more. We know from anecdotal accounts that sometimes when people with narcolepsy persist in asking for higher doses of amphetamines they are terminated as patients. Although almost any physician can be forgiven for being innocently ignorant of this matter, an unwillingness to prescribe amphetamine-based stimulants to people with narcolepsy at doses that are appropriate for them does these patients a great disservice. Often, without adequate stimulant medication patients' ability to participate safely and productively in society is seriously limited.

We hope that through this letter we will convince some physicians to begin to look into this matter. In addition, it would be helpful to have practice-based evidence studies on this topic published in the more widely read journals. As more physicians become aware that there are differences regarding drugs in patients with narcolepsy and therefore individualized treatment is needed, they will become more comfortable with prescribing adequate doses of this class of drugs to this specific patient population.

Narcolepsy is a seriously debilitating illness that brings much tragedy into the lives of those who must cope with it. Let us work together to make the medicines needed by patients with narcolepsy more available to them.

CITATION

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DISCLOSURE STATEMENT

The author is an advocate for people with narcolepsy and his opinion, while based on objective information found in the literature, is biased toward improving the welfare of that group.