



# PHARMACEUTICALS USED TO TREAT NARCOLEPSY

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This month's column will focus on the disorder of Narcolepsy and the pharmaceutical compounds employed in its treatment. Following a brief overview of the symptoms, prevalence, and pathophysiology of this disorder, we will review the pharmaceutical interventions routinely prescribed, and explore the clinical decision pathways when considering the most appropriate therapy.

Among the earliest clinical descriptions of narcolepsy were those documented by the German physician Westphal in 1877, and by Fisher in 1878. The French physician Gélinau is most frequently acknowledged as the first clinician to recognize narcolepsy as a distinct disorder. The initial descriptions included characterization of excessive daytime sleepiness and "sleep attacks". While all three documented the appearance of "sleep attacks", they did not discern symptoms of sudden muscle weakness triggered by an emotional

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event (called cataplexy), as separate from the "sleep attack" event. This is clear from the original descriptions of narcolepsy:

"I propose to give the name of narcolepsy ("narco= somnolence" and "lepsy = seized by") to a rare neurosis or at least little known until now, characterized by a mandatory need to sleep, sudden and of short duration, that recurs at more or less close intervals."

Eventually, in 1902, Loëwenfeld recognized that the emotion-induced muscle weakness was a separate feature of the disorder and coined the term "cataplexy."

Today, 130 years later, narcolepsy is characterized by a "tetrad" of clinical symptoms. Two features of the tetrad, persistent excessive daytime sleepiness and cataplexy, were documented in the original descriptions of the disorder and remain the only two clinical features essential for the diagnosis without other testing. The recognition of two additional features, hypnagogic hallucinations (the onset of dreams while still awake) and sleep paralysis (a temporary loss of muscle tone or an inability to perform voluntary movements either at sleep onset or upon awakening), were added by Yoss and Daly in 1957. Another common symptom of narcolepsy is fragmented sleep with multiple arousals and awakenings each night.

Narcolepsy may not be as rare of a disorder as once thought. According to the National Institute of Neurological Disorders and Stroke (NINDS), within the National Institutes of Health (NIH), narcolepsy is an under-recognized and under-diagnosed condition. Current estimates suggest that 1:2,000 Americans are narcoleptic. In contrast, the prevalence of narcolepsy is significantly higher in

Japan, affecting 1:600 people, but substantially lower in Israel, affecting only 1:500,000. Regardless of ethnicity, there is no gender preference. In comparison with the prevalence of other sleep disorders in the USA, narcolepsy is the third most frequently diagnosed primary sleep disorder with sleep apnea first and restless legs syndrome second [source – NINDS narcolepsy fact sheet].

The onset of narcoleptic symptoms typically occurs between the ages of 15-30, although there are reports of symptom onset occurring in very young children, as well as in adults aged 30 and above. In addition, it is not unusual for a time period of up to twelve years to elapse between the initial onset of symptoms and a definitive diagnosis.

Up to 10% of patients diagnosed with narcolepsy report that similar symptoms also exist in a close relative. In fact, the familial association of narcolepsy dates back to the very first descriptions as was noted in the mother of the narcoleptic patient first examined by Westphal, as well as the sister of Fisher's initial narcoleptic patient. This type of familial clustering led to early hypotheses of a genetic origin for this disorder. While immediate family members of narcoleptics are at a statistically increased risk of developing the disorder than the general population, this risk is low when compared with diseases that are purely genetic in origin. Regardless, most cases of narcolepsy are sporadic and occur without evidence of genetic inheritance.

Until recently, the etiology of narcolepsy was unknown but was historically associated with the specific human leukocyte antigen (HLA) allele, DQB1\*0602, most often in combination with HLA-DR2 (DRB1\*15). In the late 1990's, a team of scientists led by Thomas Kilduff discovered a group of neurons in the hypothalamus, which they named hypocretin cells. Based on the anatomy and physiology of these cells, they were hypothesized to be involved in regulation of sleep and wakefulness. In 1999, two independent groups headed by Emmanuel Mignot and Masashi Yanagisawa discovered that the clinical symptoms of narcolepsy were associated with a loss or dysfunction of hypocretin cells. This discovery revolutionized the field of sleep medicine by defining a new major neuro-chemical foundation for the state of wakefulness, and the pathophysiology of narcolepsy.

Following the initial clinical descriptions of narcolepsy in the late 1800's, various empirical treatments were employed without success. Among these were removal of cerebrospinal fluid, intra-theal air injection, and x-ray irradiation of portions of the hypothalamus. Administration of ephedrine in the early 1930's met with limited success, and did not possess the same

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level of morbidity than the previously mentioned interventions. In 1935, Prinzmetal and Bloomberg developed a new compound, Bensedrine, which was the original drug in the class to be known as "amphetamines." While originally developed to treat nasal congestion, it had no effect on the nasal mucosa. But when given orally, it led to a reduction in weight and by the mid 1940's it was routinely used as an appetite suppressant. In the following years, the stimulating effect of amphetamines on the central nervous system was discovered, and it was not long before physicians began using them to treat narcolepsy. Success in reducing the unremitting sleepiness of this disorder was significant, and led to amphetamines becoming the first line treatment for narcolepsy over the next several decades. Unfortunately, symptoms of cataplexy remained untreated and often caused significant daytime dysfunction for narcolepsy patients.

Treatment of narcolepsy with amphetamines in conjunction with compounds such as imipramine (which reduces rapid eye movement (REM) sleep, and symptoms of cataplexy) was the standard pharmaceutical intervention between the mid 1950's through the late 1980's. At that time, a non-amphetamine central nervous system stimulant, Modafinil, was developed. With a side effect profile free from addiction, tolerance, or several of the other adverse outcomes associated amphetamines, Modafinil soon found favor as the preferred wake promoting drug for narcoleptic patients. The success of CNS stimulants in promoting wakefulness has led to both dextroamphetamine and Modafinil becoming FDA-approved for alleviating symptoms of the excessive daytime sleepiness associated with narcolepsy.

In 2002, sodium oxybate, trade name Xyrem®, which is a central nervous system depressant, gained FDA approval for the treatment of both excessive daytime sleepiness and cataplexy in narcoleptic patients. The use of a CNS depressant may seem counter-intuitive as a strategy for treating excessive daytime sleepiness; however, sodium oxybate, taken immediately before sleep and again 2-4 hours later, causes an increase in slow wave sleep, a reduction the number of nocturnal awakenings, and enhanced sleep continuity. The result is a significant reduction in daytime sleepiness and cataplexy, as well as a less fragmented sleep period. The precise mechanism through which sodium oxybate reduces excessive daytime sleepiness and cataplexy is unknown, but it may involve activation of GABA<sub>B</sub> receptors as well as other receptor systems in the central nervous system.

Determining the most appropriate pharmaceutical intervention for the narcoleptic patient is influenced by a myriad of factors including age, severity of symptoms, presence or absence of cataplexy, other medical conditions and concomitant medications. For example, a young narcoleptic patient without cataplexy may achieve substantial relief from his or her symptoms by maintaining a regimented schedule of sleep onset and morning wake-up, as well as prescheduled daytime naps (when feasible). This helps to insure an adequate opportunity for sufficient sleep, and when coupled with an alerting compound such as Modafinil, may help to restore a functional level of daytime alertness. In contrast, a patient afflicted with more severe symptoms, including cataplexy, hypnagogic hallucinations and sleep fragmentation may require a more aggressive pharmaceutical paradigm. For example, in addition to good sleep hygiene, an amphetamine such as dextroamphetamine or methylphenidate may be prescribed to help sustain daytime wakefulness, along with sodium oxybate, a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant to treat cataplexy and other symptoms of REM sleep dysregulation (hypnagogic hallucinations). In a patient with sleep fragmentation sodium oxybate is often useful since sleep continuity is enhanced along with control of excessive daytime sleepiness and cataplexy.

In summary, narcolepsy is a complex disorder with multiple symptoms including excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and sleep fragmentation. The primary pharmaceutical intervention includes the use of different CNS stimulants for excessive daytime sleepiness. Symptoms of cataplexy and/or hypnagogic hallucinations require additional agents such as sodium oxybate, SSRI's or tricyclic antidepressants. Of course, non-pharmacologic therapies such as scheduled naps, regular sleep and wake schedules and proper sleep hygiene are essential elements to any successful narcolepsy treatment regime.

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