

Pharmacologic Managements of Excessive Daytime Sleepiness

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KEYWORDS

• Stimulants • Excessive daytime sleepiness • Narcolepsy • Idiopathic hypersomnia

KEY POINTS

- Excessive daytime sleepiness (EDS) is related to medical and social problems, including mental disorders, physical diseases, poor quality of life, and so forth.
- Several different types of stimulants (or wake-promoting compounds) are available to treat EDS, and a variety of new drugs are under development.
- The side effects of some of the stimulants are potent, and careful selection and managements is required.

INTRODUCTION

EDS is defined as “irresistible sleepiness in a situation when an individual would be expected to be awake, and alert.”¹ EDS has been a big concern not only from a medical but also from a public health point of view. According to recently published articles, the prevalence of patients who suffer from EDS is approximately 20% in the world.²⁻⁴ Patients with EDS have the possibility of falling asleep even when they should wake up and concentrate, for example, when they drive, play sports, or walk outside. Subjects who have EDS encounter a lower quality of life and have a higher odds ratio of developing a mental disorder, cognitive impairment, and motor vehicle accidents.⁵⁻⁸

Although nonpharmacologic treatments (ie, napping and work accommodations) are often helpful, a large majority of the diagnosed patients reported using pharmacologic therapies, mostly stimulant medications.⁹

Historically, EDS was also a large concern in the military. Many countries let soldiers take stimulants when they were engaged in military service

in World War II. Currently, preventing sleepiness caused by sleep deprivation is still a major research project by the Defense Advanced Research Projects Agency in the United States.

In 1931, the first stimulant (ie, amphetamine) was applied to treat EDS associated with narcolepsy.¹⁰ Since then, many new stimulants have developed to treat EDS, and many patients received benefits. Stimulants, however, are drugs with strong side effects (ie, sympathomimetic) and addiction potential and these treatments are mostly symptomatic; they improve the level of alertness by simply suppressing sleepiness.

Abuse potential of stimulants is a problem especially when diagnoses of hypersomnias are loosely made, and this is particularly true for narcolepsy, where stimulant abuse is rare among patients with well-defined narcolepsy.¹¹⁻¹⁴ In this article, clinical characteristics of common hypersomnias and pharmacologic treatments of each hypersomnia are described. New treatment options under development for treating EDS associated with these hypersomnias are also

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discussed. The hypersomnias focused on in this article are narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, and hypersomnia due to a medical disorder, defined in the *International Classification of Sleep Disorders, Third Edition (ICSD-3)*.

TYPES OF HYPERSOMNIAS

According to the *ICSD-3*, published in 2014, diseases that result from EDS are listed as narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome.¹⁵

This review covers the pharmacologic treatments of EDS associated with narcolepsy type 1,

narcolepsy type 2, idiopathic hypersomnia, and hypersomnia due to a medical disorder, because relatively consistent guidelines for the pharmacotherapy of these diseases are available. The *ICSD-3* diagnostic criteria of these hypersomnias are summarized in **Table 1**. For the treatment of Kleine-Levin syndrome and other hypersomnias, see the article by Arnulf.¹⁶

NARCOLEPSY

Symptoms of Narcolepsy

Narcolepsy is a syndrome characterized by “EDS that is typically associated with cataplexy and other [rapid eye movement] REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations.”¹⁷ The prevalence of narcolepsy with cataplexy has been examined in many studies and falls between 25 and 50 per 100,000 people

Table 1

Diagnostic criteria, *International Classification of Sleep Disorders, Third Edition*

Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia	Hypersomnia due to a Medical Disorder
Criteria A and B	All Criteria A–E	All Criteria A–F	All Criteria A–D
<p>A. Daily periods of irrepresible need to sleep or daytime lapses into sleep, present for at least 3 mo</p> <p>B. Either 1 or 2 or both</p> <p>1. Cataplexy and mean sleep latency ≤ 8 min and 2 or more SOREM periods on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of SOREM periods.</p> <p>2. Low CSF hypocretin-1 concentration (< 110 pg/mL or less than one-third of control values)</p>	<p>A. Daily periods of irrepresible need to sleep or daytime lapses into sleep, present for at least 3 mo</p> <p>B. Mean sleep latency ≤ 8 min and 2 or more SOREM periods on MSLT. REM within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREM periods.</p> <p>C. No cataplexy</p> <p>D. CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration is ≥ 110 pg/mL or greater than one-third of control values.</p> <p>E. The hypersomnolence and/or MSLT findings are not better explained by other causes.</p>	<p>A. Daily periods of irrepresible need to sleep or daytime lapses into sleep, present for at least 3 mo</p> <p>B. Fewer than 2 SOREM periods on MSLT (or fewer than one of nocturnal REM latency was ≤ 15 min)</p> <p>C. No cataplexy</p> <p>D. Either 1 or 2 or both</p> <p>1. Mean sleep latency ≤ 8 min on MSLT</p> <p>2. Total 24-h sleep time ≥ 660 min on 24-h polysomnographic monitoring or wrist actigraphy (averaged over ≥ 7 d)</p> <p>E. Insufficient sleep syndrome is ruled out.</p> <p>F. The hypersomnolence and/or MSLT findings are not better explained by other causes.</p>	<p>A. Daily periods of irrepresible need to sleep or daytime lapses into sleep, present for at least 3 mo</p> <p>B. The daytime sleepiness occurs as a consequence of a significant underlying medical or neurologic condition.</p> <p>C. Mean sleep latency is ≤ 8 min, and fewer than 2 SOREM periods are observed.</p> <p>D. The symptoms are not better explained by another untreated sleep disorder, a mental disorder, or the effects of medications or drugs.</p>

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