Pharmacologic Management of Daytime Sleepiness

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Excessive daytime sleepiness and abnormal sleep-wake patterns are becoming increasingly pervasive in modern society. The major causes of excessive daytime sleepiness include pathologic abnormalities of the central nervous system, such as narcolepsy and idiopathic hypersomnia; deficiencies in quality or quantity of sleep, such as those caused by sleep apnea and poor sleep hygiene; disturbances to the body's natural circadian rhythm, such as those caused by shift work or jet lag; and drugs, which can increase sleepiness either therapeutically or as a side effect. Determining the cause of daytime sleepiness is the first step in treating it. Setting appropriate and realistic treatment goals with the patient and initiating treatment are the next steps. Although the medications available to improve daytime wakefulness (e.g., amphetamines, methylphenidate, pemoline, and modafinil) are effective, they are not a substitute for sleep. Finally, timely follow-up is necessary to monitor treatment adherence, response, and side effects. *(J Clin Psychiatry 2004;65[suppl 16]:46–49)*

Although some disorders, such as narcolepsy and obstructive sleep apnea syndrome, are typically recognized as classic causes of excessive sleepiness, a number of other causes exist. For example, idiopathic hypersomnia (sometimes called non–rapid eye movement narcolepsy), a disorder in which the patient experiences excessive sleepiness and prolonged sleep at night, and posttraumatic hypersomnia, a disorder that develops as the result of physical injury or disease in the central nervous system, may cause excessive daytime sleepiness. Psychiatric medications and drugs used for chronic pain may also cause excessive daytime sleepiness. Daytime sleepiness is a common problem for patients with obstructive sleep apnea who use continuous positive airway pressure (CPAP) therapy.[1,2] Shift work sleep disorder, one of the circadian rhythm sleep disorders,[3] is associated with transient insomnia or excessive sleepiness caused by changes in work schedules or scheduled work times that are incompatible with nonwork sleep-wake cycles. Finally, insufficient sleep and poor or inadequate sleep hygiene can cause excessive daytime sleepiness. Because the causes of excessive daytime sleepiness are many and varied, it is important for clinicians to adequately assess and properly diagnose this debilitating disorder.

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Excessive sleepiness interferes with functioning at home and at work, and sleepy individuals may pose a potential danger to themselves and others, especially while working or driving motor vehicles.[4,5] Proper diagnosis (which may include an all-night polysomnogram), setting treatment expectations with the patient, initiating treatment, and providing follow-up care are key components of managing patients with excessive sleepiness.

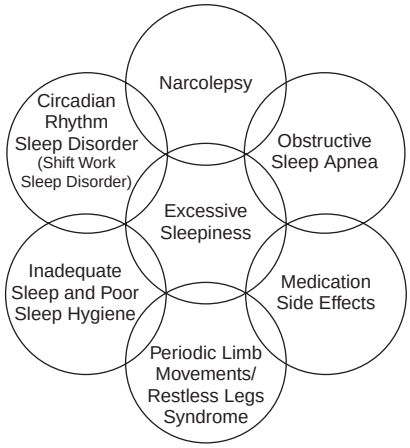
NONPHARMACOLOGIC TREATMENT

Although medications are helpful in the treatment of daytime sleepiness, nonpharmacologic treatment may help to optimize treatment response. Many patients with a sleep disorder get insufficient sleep, have poor or inadequate sleep hygiene, or have a secondary sleep disorder. Some patients may need to be counseled to make lifestyle changes to develop better sleep habits. The presence of a secondary sleep disorder, if not properly diagnosed and treated, could lead to partial symptom relief initially, but ongoing daytime sleepiness (Figure 1). Discussing sleep habits with patients is an important first step in making a proper diagnosis and setting appropriate treatment goals.

TREATMENT GOALS

Improving alertness is the primary goal of therapy. The benefits of successful treatment include a return to normal functioning at work, school, and home and in social interactions. Additional goals of treatment should be to minimize side effects and to ensure that the dosing regimen facilitates adherence (once-a-day dosing is ideal). Setting appropriate, realistic expectations with the patient is of paramount importance to reaching treatment goals. Clinicians must communicate what medication can and cannot

Figure 1. Overlap in Sleep Disorders Associated With Excessive Sleepiness



do, with the caveat that taking wake-promoting medication does not replace the need for sleep. The restorative aspects of sleep are essential to improving wakefulness and alertness during the day.[3]

PHARMACOLOGIC TREATMENT

A consensus statement for the treatment of narcolepsy has been published by the American Sleep Disorders Association (ASDA)[6] and revised,[7] but no definite consensus on the proper treatment of all aspects of excessive daytime sleepiness exists. Nonetheless, since excessive daytime sleepiness is the most disabling symptom of narcolepsy, many of the practice parameters set forth for treating narcolepsy are relevant for treating patients with excessive daytime sleepiness. A review[8] of stimulant use based on the ASDA standards of practice for narcolepsy reported that stimulants improved daytime alertness in 65% to 85% of patients with narcolepsy, while 15% to 35% of patients reported minimal or no improvement in wakefulness (owing to lack of efficacy, side effects, or other factors). Although clinicians rely heavily on past experience (both successes and failures) in making treatment choices for their patients, many tend to prescribe a dosage of medication that is too low to optimally treat the patient. Sometimes clinicians limit therapy choices on the basis of side effects seen in previous patients.

Several medications have been studied for their efficacy in enhancing daytime wakefulness. Amphetamines were developed in the 1930s and were the first treatment for daytime sleepiness and narcolepsy. Methylphenidate became available in the 1950s, and then pemoline became available in the 1970s. The most recent medication introduced for managing excessive sleepiness, modafinil, became available in 1999. γ-Hydroxybutyric acid (GHB), although currently indicated only for the treatment of cataplexy, has also been found to improve daytime alertness[9,10] and is under investigation for future treatment.

Amphetamines

Amphetamines—including mixed amphetamine salts—are a mainstay of treatment for narcolepsy and have a long record of efficacy, despite the fact that few studies have been performed.[7] The benefit-to-risk ratio is not well documented because the published clinical trials included only a small number of patients.[11,12] Although primarily used in narcolepsy, amphetamines, used properly, increase alertness and physical energy and, therefore, may be useful in controlling excessive daytime sleepiness. Patients taking amphetamines, especially at high doses, may develop tolerance and consequently require higher and higher doses to sustain improved wakefulness. Amphetamines are considered to have abuse potential and should be used with caution.

Methlyphenidate

Psychiatrists are familiar with methylphenidate as a treatment for attention-deficit/hyperactivity disorder (ADHD), particularly in children. Methylphenidate also has a long record of clinical efficacy in the treatment of excessive sleepiness despite the fact that only small clinical trials have been published.[13] As with amphetamines, few studies exist that examine the efficacy of methylphenidate in patients with excessive sleepiness. Nonetheless, methylphenidate is indicated for use in narcolepsy.

Pemoline

Like methylphenidate, pemoline is a treatment for ADHD in adults and in children over the age of 6 years. Unlike methylphenidate, pemoline carries a risk of hepatotoxicity, which, although rare, can be fatal. Pemoline should not be considered as first-line therapy.[14,15]

Despite the lack of large, controlled trials of pemoline for sleepiness, one small clinical trial[16] reported its efficacy when used on an occasional basis to improve alertness and performance during a night shift. The use of pemoline in patients with excessive sleepiness is contraindicated by the U.S. Food and Drug Administration due to the risk of hepatotoxicity.[7]

Modafinil

Modafinil is the newest and most-studied medication for the treatment of excessive sleepiness associated with narcolepsy,[17,18] obstructive sleep apnea with persistent sleepiness despite CPAP therapy,[19,20] and shift work sleep disorder.[21] Modafinil is the only wake-promoting agent approved for use in the latter 2 indications. Furthermore, large multicenter studies[18,22–24] have documented a favorable benefit-to-risk ratio for modafinil, and its efficacy and safety[18] are supported by open-label experience.

γ-Hydroxybutyric acid

γ-Hydroxybutyric acid is a naturally occurring substance that has been synthesized as sodium oxybate (available in liquid form) and is currently only indicated for the treatment of cataplexy associated with narcolepsy.[25] Although GHB is not indicated as a primary treatment for daytime sleepiness, several studies[9,10,26,27] have shown a reduction in the number of naps taken among patients taking GHB for narcolepsy. γ-Hydroxybutyric acid is usually taken at bedtime and repeated 2 or 3 hours later.

SIDE EFFECTS OF PHARMACOLOGIC TREATMENT

Clinicians should watch carefully for side effects when treating a patient with stimulants. The most common side effects are related either to the central nervous system (e.g., headache, tremor, anxiety, and mood changes) or to the cardiovascular system (e.g., changes in blood pressure, arrhythmia, and angina). One concern is that tolerance may develop, particularly with amphetamine or methylphenidate, and the dosages may need to be increased. Higher doses, in turn, may lead to an increase in frequency and severity of side effects.

FOLLOW-UP

Regular follow-up (beginning within the first few weeks after initiating treatment with medication) is necessary to monitor treatment response and side effects. Thereafter, regular checkups at least every 6 months should be scheduled to gauge the effectiveness of the medication, to ensure response and adherence, and to screen for other sleep disorders that the patient may have had before beginning treatment or may have developed during treatment. Clinicians should check for a worsening of sleep disturbances, the development of new sleep problems (e.g., insomnia), and any changes in mood. Since adherence is inversely proportional to the number of doses per day, once-a-day dosing is the most desirable. Because of the risk of decreased adherence, prescribing a medication that requires more than 2 doses a day should be avoided if possible. Patients who fail to respond to medication should be reassessed for other possible sleep disorders, insufficient sleep, and poor sleep hygiene.

SUMMARY

Patients with excessive daytime sleepiness suffer from impaired quality of life. Narcolepsy, medication-induced sleepiness, obstructive sleep apnea with residual somnolence, and poor or inadequate sleep hygiene are just some of the possible causes of excessive daytime sleepiness. The first step in managing excessive sleepiness is determining the cause. Next, setting treatment goals and clarifying expectations with the patient are essential to promoting adherence even before treatment begins. Once treatment is initiated, regular follow-up is essential to ensure that the treatment plan is effective and well tolerated.

Drug names: amphetamine and dextroamphetamine (Adderall and others), dextroamphetamine (Dexedrine and others), methamphetamine (Desoxyn and others), methylphenidate (Ritalin, Concerta, and others), modafinil (Provigil), pemoline (Cylert and others), sodium oxybate (Xyrem).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, γ-hydroxybutyric acid is not approved by the U.S. Food and Drug Administration for the treatment of daytime sleepiness.

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