Sleep, 17(4):348–351

ASDA Standards of Practice

Practice Parameters for the Use of Stimulants in the Treatment of Narcolepsy

Standards of Practice Committee of the American Sleep Disorders Association

This is a publication from the American Sleep Disorders Association. It has been reviewed and edited by the Board of the ASDA. It reflects their recommendations for the practice of sleep medicine in North America.

Summary: Narcolepsy is a disorder of the central nervous system characterized by excessive sleepiness, cataplexy, and other rapid-eye-movement (REM)-sleep phenomena such as sleep paralysis and hypnagogic hallucinations. Although stimulants are the only effective treatment for the sleepiness of narcolepsy, no clinical guidelines on the use of stimulants in the treatment of narcolepsy have been published that address the following factors: appropriate doses; development of tolerance; potential for side effects, adverse reactions and abuse; and use in children and pregnant or breast-feeding women. These practice parameters from the American Sleep Disorders Association provide the first clinical guidelines on the appropriate use of stimulants in the treatment of narcolepsy. **Key Words:** Cataplexy—Narcolepsy, therapy—Narcolepsy, drug therapy—Sleep disorders, drug therapy—Pharmacology—Sleep, REM—Sleep—sleep disorders.

Narcolepsy is a central nervous system disorder characterized by excessive sleepiness, cataplexy and other rapid-eye-movement (REM)-sleep phenomena such as sleep paralysis and hypnagogic hallucinations. Although stimulants are the only effective treatment for the sleepiness of narcolepsy, no clinical guidelines on the use of stimulants in the treatment of narcolepsy have been published that address the following factors: appropriate doses; development of tolerance; potential for side effects, adverse reactions and abuse; and use in children and pregnant or breast-feeding women. Although the United States Food and Drug Administration (FDA) has approved only methylphenidate hydrochloride and dextroamphetamine sulfate for the treatment of narcolepsy in the U.S.A., several other stimulants are used clinically, and the FDA's recommended doses are often exceeded in clinical practice. Other clinical concerns exist regarding the effectiveness of treatment with stimulants for individuals who must maintain alertness for safe operation of motor vehicles, effective employment and satisfactory social and home activities. Although narcolepsy is a chronic disorder, limitations on dispensing of medications and extensive prescribing documentation sometimes interfere with the patient's ability to receive appropriate treatment.

This report provides the first clinical guidelines on the appropriate use of stimulants in the treatment of narcolepsy. Idiopathic hypersomnia is not specifically addressed in this paper, but many of the following guidelines also apply to this disorder [1.1,4.3].[1] The American Sleep Disorders Association (ASDA) expects these guidelines to have an impact on professional behavior, patient outcomes and, possibly, healthcare costs. Adherence to these guidelines is voluntary. These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician in light of the individual circumstances presented by the patient.

METHODS

The Standards of Practice Committee of the ASDA appointed a task force to review the scientific literature

Accepted for publication August 1993.
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[1] This position paper is referenced by the square-bracketed numbers to the numbered paragraphs in the accompanying review.

on the use of stimulants in the treatment of narcolepsy (1). On the basis of the accompanying review and after consultation with other specialists and interested parties, the subsequent recommendations were developed by the Standards of Practice Committee and approved by the Board of Directors of the ASDA. All authors and ASDA Board members completed detailed conflict of interest statements and were found to have no conflicts of interest with regard to this topic.

This paper will be reviewed as necessary, and the recommendations updated in accordance with new scientific information.

BACKGROUND

The symptoms of narcolepsy include excessive sleepiness and cataplexy that often produce severe functional impairment. Narcolepsy is a disorder of the central nervous system, most likely caused by impaired neurotransmitter function, and has a strong association with the human leukocyte antigens (HLA) HLA-DQ1 and HLA-DR2 (or as in the new HLA nomenclature, HLA-DQ6 and HLA-DR15). However, HLA testing alone does not establish a diagnosis of narcolepsy. Although narcolepsy has characteristic clinical symptoms, physical findings of the disorder are rarely observable. Diagnosis rests upon subjective symptoms and the results of electrophysiologic tests of polysomnography followed by multiple sleep latency testing. The severity of narcolepsy is reflected by the severity of the sleepiness, cataplexy, or both. Sleepiness is severe when the sleepiness is present daily and during physical activities that require mild to moderate attention; it is usually associated with a mean sleep latency on the multiple sleep latency test (MSLT) of less than 5 minutes (2).

Treatment aims are to improve daytime alertness with stimulant medications and to suppress cataplexy with other agents, usually tricyclic antidepressants or seratonin-reuptake inhibitors. Stimulants alone have little if any effect on cataplexy. The effects of stimulant medications are not limited to the improvement of alertness but include stimulation of cardiovascular and other systems; therefore, side effects and adverse reactions are not uncommonly reported. Medications and dose recommendations vary widely among different authors.

The review article accompanying this position paper addresses the issue of stimulant use in narcolepsy and explores the available scientific information. The following recommendations are based upon the information contained in the review article whenever possible and, when such information does not exist, upon consensus opinion.

RECOMMENDATIONS

1. Diagnosis

An accurate diagnosis of narcolepsy should be established before commencing treatment with stimulant medications [4.2].

For all patients suspected of having narcolepsy, an all-night polysomnogram followed by an MSLT is indicated to confirm the diagnosis, ascertain the presence of concurrent sleep disorders and determine the severity of sleepiness (3). The diagnosis of narcolepsy should not depend solely on the patient's subjective complaints. Detailed diagnostic criteria include the evaluation of clinical symptoms in conjunction with specific findings of electrophysiologic tests or witnessed cataplexy, a pathognomonic clinical feature of narcolepsy. Cataplexy, however, is rarely witnessed by the physician.

2. Treatment objectives and indications

(a) The objective of treatment with stimulants should be to alleviate daytime sleepiness, thereby allowing the fullest possible return of normal function for patients at work, at school and at home [1.0].

(b) Stimulants are most effective at producing improvement in fatigue and sleepiness in boring and inactive situations; there is no evidence that fully alert individuals have enhanced maximal performance of complex attention tasks when using stimulants [5.3].

(c) Patients with severe sleepiness should be advised to avoid potentially dangerous activities at home and at work, and they should not operate a motor vehicle until their sleepiness is appropriately controlled by stimulant medications [4.2].

(d) Stimulant medications need not be prescribed for all patients with narcolepsy as there is variation in the severity of patients' sleepiness, their life styles and their abilities to cope with symptoms [1.0,4.4,7.0].

3. Effective medications

(a) Pemoline, methylphenidate hydrochloride, dextroamphetamine sulfate, methamphetamine hydrochloride and modafinil are effective for the treatment of sleepiness in patients with narcolepsy [4.4]. Modafinil is not currently available in the U.S.A. The prescription of methamphetamines is restricted in some states.

(b) Methamphetamine hydrochloride generally produces the most improvement in alertness and has the most rapid onset of action. Dextroamphetamine sulfate and methylphenidate hydrochloride are only slightly less effective. Pemoline has less alerting effect than the other medications [4.4,5.2]. However, the relative alert-

ing effects of these medications in individual patients is unpredictable.

4. Dosage

(a) Treatment in adults should commence with low doses of stimulants not to exceed a total daily dose of: pemoline, 37.5 mg; methylphenidate hydrochloride, 30 mg; dextroamphetamine sulfate, 15 mg; and methamphetamine hydrochloride, 15 mg [4.3,4.5,4.10].

Patients have a wide variation in response to stimulants and in the incidence of side effects; therefore, initial doses should be low and increased depending upon individual patient response, incidence and tolerance of side effects, and the patient's work and lifestyle needs.

(b) Full therapeutic response in adult patients with narcolepsy can usually be obtained with daily medication doses below the recommended maximal doses of: pemoline, 150 mg; methylphenidate hydrochloride, 100 mg; dextroamphetamine sulfate, 100 mg; and methamphetamine hydrochloride, 80 mg [4.3,4.7,4.10].

(c) A combination of long- and short-acting forms of stimulant medications may be effective for some patients [4.10].

The effects of pemoline typically last 8–10 hours, and the medication is usually given once or twice per day, with the second dose given no later than midday. Pemoline is sometimes combined with a single dose or multiple doses of methylphenidate hydrochloride or dextroamphetamine sulfate. Methylphenidate hydrochloride typically has effects that last 3–4 hours and is usually given in divided doses. Amphetamines usually last 6–10 hours and may be given in divided doses. Sustained-release forms of methylphenidate hydrochloride and dextroamphetamine sulfate are available. As with any medication, stimulants may require some trial and error of dosage and timing to achieve maximum effectiveness.

5. Tolerance

(a) Of the stimulants used to treat narcolepsy, amphetamines, especially at high doses, are the most likely to result in the development of tolerance [4.8,5.4].

(b) Patients who fail to respond to adequate doses of stimulant medication should be carefully assessed for other sleep disorders, such as insufficient sleep, inadequate sleep hygiene, an irregular sleep-wake pattern, obstructive sleep apnea syndrome or periodic limb movement disorder, that may contribute to excessive sleepiness [4.8].

6. Abuse

(a) Patients with narcolepsy are no more likely to become drug abusers or to use stimulant medications illicitly than any other group of patients treated with stimulants [5.5].

Patients for whom stimulants are prescribed may face lifelong commitments to medication; therefore, great care should be taken to avoid an erroneous diagnosis.

(b) Of the stimulants used to treat narcolepsy, methamphetamine hydrochloride and dextroamphetamine sulfate are more likely to be sought and used illicitly than methylphenidate hydrochloride. Pemoline has the least potential for abuse.

7. Side effects

Most patients with narcolepsy can be effectively treated with stimulants without developing significant side effects.

Common side effects of stimulants include headache, irritability, nervousness or tremulousness, hyperhidrosis, anorexia, insomnia, gastrointestinal complaints, dyskinesias and palpitations. Doses of methylphenidate hydrochloride or dextroamphetamine sulfate greater than 60 mg per day are likely to produce disturbed nocturnal sleep [4.5]. Pemoline can cause altered liver function.

Little evidence suggests that stimulants in therapeutic doses cause a significant increase in blood pressure in normo- or hypertensive patients. However, periodic measurements of blood pressure are advisable [4.5].

Patients who use amphetamines at higher than recommended doses are at greatest risk of developing psychiatric, cardiovascular and cerebrovascular complications of stimulant use [4.5,4.7].

8. Use in pregnancy

Stimulants should only be used during pregnancy when the potential benefits to the patient are judged to clearly outweigh the risks to the fetus [4.9]. Most patients should be advised to reduce or discontinue stimulants during attempts at conception and for the duration of pregnancy.

The FDA classifies drugs as A, B, C, D or X, indicating increasing levels of toxicity, according to their embryotoxic and teratogenic effects. Dextroamphetamine sulfate, with a D classification, and methamphetamine hydrochloride, with a C classification, are contraindicated during conception and pregnancy. Pemoline, classified as a B-category medication, produces no fetal injury in animal studies, but there have been no controlled studies in humans. Methylphenidate hydrochloride has no classification because no

adequate animal or human studies have been performed. The morbidity of sleepiness and the mother's risk of suffering an accident as a result of sleepiness need to be weighed against the fetus' possible risk of problems as a result of exposure to intrauterine stimulants.

9. Use in children

(a) Stimulants can be used safely for the treatment of narcolepsy in children [4.6].

Usual maximal doses of stimulants for prepubertal or early adolescent children are pemoline, 112.5 mg, or methylphenidate hydrochloride, 30 mg [4.6]. Stimulants used in therapeutic doses do not affect emotional stability or subsequent adult height [4.6].

(b) Nursing mothers who have narcolepsy may require low doses of stimulants to maintain their wakefulness, but caution is urged [4.7].

Complications among breast-fed children whose mothers use stimulants have not been reported in the literature, but the potential for complications does exist, and, therefore, caution is urged. The breastmilk of nursing mothers contains a three- to sevenfold higher concentration of stimulant medication than is present in the mothers' plasma.

10. Alternative therapies

(a) Intermittent withdrawal of medication (drug holiday) is of unproven benefit to the patient [4.10].

There are no studies to document prevention of tolerance by intermittent withdrawal of medication. Some patients require continuous treatment with stimulants.

(b) Little evidence supports the use of propranolol hydrochloride, L-tyrosine, codeine sulfate, gamma-hydroxybutyrate, protriptyline hydrochloride, viloxazine or ritanserin in the treatment of the sleepiness of narcolepsy [3.6].

(c) Naps can be helpful to temporarily control the sleepiness of narcolepsy, but ad libitum sleep and improved nocturnal sleep have not been shown to replace the need for stimulant medications in most patients with narcolepsy [3.5].

Even when stimulants are used, a nap may be recommended before patients perform potentially dangerous activities such as operating a motor vehicle.

11. Follow-up

(a) A patient stabilized on stimulant medication should be seen by a physician at least once per year, and preferably once every 6 months, to assess the development of medication side effects, including sleep disturbance, mood changes and cardiovascular or metabolic abnormalities.

(b) Patients taking pemoline should have liver function tests at the start of treatment, approximately 4 weeks after the initiation of treatment, at least once per year, and when there is any change in health that might suggest an alteration in liver function [4.5].

(c) Polysomnographic reevaluation of patients with narcolepsy should be considered if symptoms of sleepiness increase significantly or if specific symptoms develop that suggest new or increased sleep abnormalities as might occur in disorders such as sleep apnea or periodic limb movement disorder.

(d) Continued prescription of stimulant medication by telephone or mail is not recommended if the patient has not been seen by the prescribing physician within the prior 12 months.

Acknowledgements: The Standards of Practice Committee comprises Michael Thorpy, M.D., Director, Sleep-Wake Disorders Center, Montefiore Medical Center, and Associate Professor of Neurology, Albert Einstein College of Medicine, Bronx, NY; Andrew Chesson, M.D., Director, LSUMC Sleep Disorders Center, Shreveport, and Professor of Neurology, Louisiana State University, Shreveport; Richard Ferber, M.D., Director, Center for Pediatric Sleep Disorders, Children's Hospital, Boston, MA, and Assistant Professor of Neurology, Harvard Medical School; Gihan Kader, M.D., Director, HCA-Wesley Neurodiagnostic and Sleep Disorder Center, Wichita, KS, and Assistant Professor of Psychiatry and Internal Medicine (Neurology), University of Kansas School of Medicine; Richard Millman, M.D., Director, Sleep Disorders Center, Rhode Island Hospital, Providence, RI, and Associate Professor of Medicine, Brown University; Martin Reite, M.D., Director of Nonrespiratory Sleep Disorders at the National Jewish/University of Colorado Sleep Disorders Center, Denver, CO, and Professor of Psychiatry, University of Colorado Health Sciences Center; Philip Smith, M.D., Medical Director, The Johns Hopkins Sleep Disorders Center, and Associate Professor of Medicine, The Johns Hopkins School of Medicine; Virgil Wooten, M.D., Associate Director, Sleep Disorders Center, Sentara Norfolk General Hospital, Norfolk, VA, and Associate Professor of Medicine and Psychiatry, Eastern Virginia Medical School.

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