BRIEF COMMUNICATION

Lisdexamfetamine to improve excessive daytime sleepiness and weight management in narcolepsy: a case series

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Objective: To report the successful use of lisdexamfetamine in the management of narcolepsy.

Methods: Five narcoleptic patients received lisdexamfetamine, at different dosages and for different periods, for management of excessive daytime sleepiness and weight control.

Results: All patients experienced improvement of excessive daytime sleepiness and lost weight without side effects.

Conclusion: Lisdexamfetamine appears promising for the treatment of two of the most common symptoms of narcolepsy: excessive daytime sleepiness and weight gain.

Keywords: Sleep; excessive daytime sleepiness; weight gain; obesity; narcolepsy; lisdexamfetamine

Introduction

Narcolepsy is a rare hypothalamic disease and sleep disorder characterized by excessive daytime sleepiness (EDS) and uncontrollable episodes of falling asleep regardless of the circumstances.1 Other symptoms include abnormalities during the rapid eye movement (REM) stage of sleep, such as cataplectic attacks, sleep paralysis, and hypnagogic and hypnopompic hallucinations.1,2 Disease onset is characterized by a bimodal distribution, usually starting around adolescence or early adult life, but with the potential to occur at any age.3-5 According to the International Classification of Sleep Disorders, 3rd edition (ICSD-3), narcolepsy type 1 (NT1) is characterized by excessive daytime sleepiness, hypocretin deficiency syndrome, and signs of REM-sleep dissociation (e.g., cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis). Narcolepsy type 2 (NT2) is characterized by excessive daytime sleepiness and abnormal manifestations of REM sleep on polysomnography/multiple sleep latency test (MSLT); cataplexy must be absent and the CSF hypocretin-1 concentration must be greater than 110 pg/mL.6

The pathophysiology of the selective loss of hypocretinergic neurons is uncertain, but inflammatory/autoimmune processes appear to be substantially involved. EDS represents the most common and disabling symptom, with episodes of irresistible, typically short and restorative sleep attacks.7,8

Narcolepsy has a major impact on the activities of daily living.9 These patients experience many limitations and difficulties, especially in daytime activities such as school, work, interpersonal relationships, and social activities.10 This decreases quality of life and is associate with a higher risk of accidents in situations requiring attention, such as driving or manual labor.11

The primary objective of narcolepsy management should be to alleviate daytime sleepiness and restore the patient’s function as close to normal as possible at school, at work, at home, and socially.12

The first-line of therapy for EDS in narcolepsy consists of psychostimulants and sodium oxybate.13 In some cases, EDS may persist despite treatment, especially when adverse effects occur and optimal dose titration is difficult. In addition, critical concerns such as weight gain leading to obesity affect about 30% of narcolepsy patients.14

Few medications have been approved to treat EDS; these include methylphenidate, amphetamines, modafinil, and sodium oxybate.15 Others have not been approved for this indication but are prescribed off-label, such as lisdexamfetamine. Although this central nervous system stimulant has not been approved by regulatory agencies for narcolepsy, it has been used to managing narcolepsy symptoms with good tolerability.16 Lisdexamfetamine dimesylate is a prodrug of dextroamphetamine which permits once-daily oral administration. It is not recommended for

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weight loss as monotherapy, but has been used for this purpose. As sodium oxybate has not yet been approved by the Brazilian Health Surveillance Agency (ANVISA), pharmacotherapeutic options for treatment of narcolepsy are limited in the country. We report a series of five patients with narcolepsy who started lisdexamfetamine after failure of modafinil and methylphenidate and describe the potential of this agent for management of EDS and narcolepsy-associated obesity.

Case series

This report describes five patients treated at the Universidade Federal de São Paulo Outpatient Excessive Daytime Sleepiness Clinic. All patients (four women and one man, ages 22-51 years) met ICSD-3 diagnostic criteria for narcolepsy, including an average sleep latency of ≤8 minutes and presence of two or more episodes of sleep-onset REM periods (SOREMP). Two cases were classified as NT1 and three as NT2; CSF hypocretin-1 levels were measured in four of the five patients (Table 1). All patients had been taking stimulant medication (methylphenidate or modafinil) for treatment of EDS for at least 3 months and were on stable doses. The decision to start lisdexamfetamine was prompted by refractory EDS in all cases. The dosage was individualized, but generally did not exceed 50 mg.

The duration of lisdexamfetamine therapy ranged from 2 to 20 months (median, 3 months). Each patient had EDS quantified by the Epworth Sleepiness Scale (ESS) before and after initiation of lisdexamfetamine.

Patient #1 was a 28-year-old male with NT2 and a history of restless legs syndrome. Lisdexamfetamine was administered for 2 months at a dosage of 50 mg in the morning, with improvement in somnolence and slight weight loss (Table 1).

Patient #2 was a 22-year-old female with NT2 and a history of restless legs syndrome. Lisdexamfetamine was administered for 3 months at a dosage of 50 mg in the morning, with improvement in somnolence and progressive weight loss (Table 1).

Patient #3 was a 27-year-old female with NT2. Lisdexamfetamine was given for 5 months at a dosage of 50 mg in the morning, with improvement in EDS, reductions in appetite and sugar cravings, and progressive weight loss (Table 1).

The only patient who gained weight was patient #4, a 51-year-old postmenopausal female with NT1. Lisdexamfetamine was administered for 2 months at a dosage of 30 mg/day, also in the morning. At the start of treatment, patient #4 reported a reduction in appetite, but at her last visit, 2 months after starting lisdexamfetamine, she reported increased appetite resulting in weight gain. Curiously, she was the only patient whose daytime sleepiness decreased only slightly (ESS: 23 at baseline vs. 20 after treatment), with no clinical relevance. In addition, she reported an increase in hallucinations, asthenia, occasional chest pain, and generalized malaise.

Patient #5 was a 44-year-old female with NT1 and a history of polycystic ovary syndrome. Lisdexamfetamine was administered for 20 months at a dosage of 50 mg in the morning, combined with citalopram 20 mg/day. EDS improved and there was progressive weight loss (Table 1). One month after initiation of lisdexamfetamine, patient #5 reported psychomotor slowing, which resolved spontaneously. This patient had the longest duration of lisdexamfetamine therapy (20 months) and lost the most weight (down to 85 kg at treatment from 101 kg at baseline). Her ESS score also improved markedly, from 15 at baseline to 5 after treatment.

Overall, all five patients in this series reported improvement of EDS. ESS scores decreased from a mean of 18.2 at baseline to 10.8 after at least 8 weeks of lisdexamfetamine treatment (Table 1). During the evaluation period, all patients reported appetite reduction; four experienced weight loss and one experienced weight gain.

Regarding safety, irritability was reported by two of the five patients in this series; one complained of psychomotor slowing, disconnected thinking, and headache. One patient denied any adverse effects and, in fact, reported improvement in anxiety symptoms.

Ethics statement

This investigation was approved by the ethics committee of Universidade Federal de São Paulo (CEP/UNIFESP 3348735, project 0286/2019, CAAE 0182119.1.0000.5505).

Discussion

In our case series, lisdexamfetamine improved EDS as soon as the first month of use and up to 20 months after

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### Table 1 Clinical characteristics of the sample before and after intervention with lisdexamfetamine

| Patient | Age | Gender | Narcolepsy type | HCT-1 (pg/mL) | SOREMP | MSLT (mins) | Maximum dose (mg) | Treatment duration (months) | BMI (kg/m²) | Epworth Sleepiness Scale |
|---------|-----|--------|-----------------|--------------|--------|-------------|-------------------|--------------------------|-------------|----------------------------|
| #1      | 28  | M      | NT2             | 2            | 350    | 2           | 7"                | 50                       | 2           | 28.4                       | 27.7          | 19                        | 10             |
| #2      | 22  | F      | NT2             | 2            | 305    | 4           | 1'48"             | 50                       | 3           | 28.8                       | 26.8          | 19                        | 8              |
| #3      | 27  | F      | NT1             | 2            | NM     | 2           | 8"                | 50                       | 5           | 28                         | 24            | 15                        | 11             |
| #4      | 51  | F      | NT1             | 1            | 58     | 3           | 1'5"              | 30                       | 2           | 26.6                       | 28.2          | 23                        | 20             |
| #5      | 44  | F      | NT1             | 1            | 40     | 4           | 5"                | 50                       | 20          | 36.2                       | 30.4          | 15                        | 5              |

BMI = body mass index; F = female; HCT-1 = hypocretin-1; M = male; MSLT = multiple sleep latency test; NM = not measured; SOREMP = sleep-onset rapid eye movement episodes.

Epworth Sleepiness Scale scores range from 0-24; 0-9 indicates no sleepiness symptoms, while > 10 indicates daytime sleepiness.
initiation of therapy, as well as reduced appetite and promoted weight loss.

Patients with narcolepsy have several clinical comorbidities, but weight gain is particularly common, often leading to obesity (30% of cases). This, in turn, is associated with the metabolic syndrome and increased cardiovascular risk, which can significantly reduce quality of life and increase morbidity and mortality. Evidence suggests that narcolepsy is associated with weight gain regardless of disease duration or type.\textsuperscript{14,19,20} Reduced hypocretin levels, basal metabolism, and physical activity can explain this finding at least partly; narcoleptic patients are at 50% higher risk of developing overweight and obesity than the general population.\textsuperscript{21} In addition, weight gain may be related to an increasing and alarming prevalence of eating disorders, with 50% of narcoleptic patients reporting constant food cravings and an increased prevalence of binge eating.\textsuperscript{22,23} The mechanisms underlying weight gain in narcolepsy are still unknown, and we hope these reflections will help drive a new line of research into this rare and disabling disease. Although the small sample size precluded any statistical comparisons, this series suggest that lisdexamfetamine is well tolerated and can be an option for management of EDS and body weight in patients with narcolepsy.

An additional limitation of this study was its retrospective approach. However, there are no other published data on lisdexamfetamine as an option to treat EDS in narcolepsy. Large, randomized trials are needed to validate our empirical observations. Ideally, such studies would include dietary recalls, investigation of eating habits, and bioelectrical impedance assessment of body composition. Positive findings could lead to a formal indication of lisdexamfetamine as an alternative treatment option for EDS and obesity in patients with narcolepsy.

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Disclosure

The authors report no conflicts of interest.

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