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SCIENTIFIC INVESTIGATIONS

Treatment of severe morning sleep inertia with bedtime long-acting bupropion and/or long-acting methylphenidate in a series of 4 patients

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Study Objectives: To assess the benefit of bedtime long-acting bupropion and/or long-acting methylphenidate in the therapy of severe morning sleep inertia (SI), a chronic condition that has major adverse consequences on level of functioning and quality of life, and for which there is no recognized therapy.
Methods: Patients underwent clinical interviews and examinations and completed comprehensive questionnaires. They underwent overnight video-polysomnography and next-day multiple sleep latency testing (apart from 1 case with obstructive sleep apnea). Treatments are described in the case reports.
Results: Case 1, a 16-year-old girl who was very late to school every day from severe morning SI despite obstructive sleep apnea being fully controlled with continuous positive airway pressure therapy, responded to bedtime bupropion-extended release (xl) 150 mg, together with methylphenidate-sr (sustained release), 36 mg (along with 20 mg methylphenidate taken 1 hour before the alarm would go off). She woke up in a timely fashion and has started her classes on time, with benefit maintained at 6-month follow-up. Case 2, a 29-year-old female with idiopathic hypersomnia and major depression and associated severe morning SI while maintained on 20 mg twice-daily generic Adderall, responded immediately (first night) to bedtime bupropion-xl, 150 mg, with benefit maintained at the 4-month follow-up. Case 3, a 74-year-old man with idiopathic hypersomnia and major depression maintained on daily methylphenidate-sr and direct-release methylphenidate, along with 300 mg bupropion-xl, developed progressively severe morning SI that immediately responded to changing his bupropion-xl regimen to 150 mg nightly and 150 mg every morning, with benefit maintained at the 3-year follow-up. Case 4, a 60-year-old female with idiopathic hypersomnia and severe morning SI, was immediately intolerant to bedtime bupropion-xl, which was discontinued.
Conclusions: Bedtime use of long-acting bupropion and/or long-acting methylphenidate can be effective in the therapy for severe morning SI and warrants further clinical use along with systematic research.
Keywords: sleep inertia, idiopathic hypersomnia, bupropion, methylphenidate, depression, psychiatric disorders, obstructive sleep apnea, delayed sleep phase syndrome
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BRIEF SUMMARY
Current Knowledge/Study Rationale: A reliable effective therapy for severe morning sleep inertia remains to be identified. A consecutive series of 4 treated cases with sleep inertia is presented, with complete sustained response to long-acting bupropion and/or long-acting methylphenidate taken at bedtime in 3 cases, and with 1 case being intolerant to bupropion-sr.
Study Impact: Long-acting bupropion and/or long-acting methylphenidate taken at bedtime hold promise as effective therapy for severe morning sleep inertia. Further clinical experience with this therapy is encouraged, along with systematic studies.

INTRODUCTION

Severe morning sleep inertia (SI) was formally described by the Czech sleep neurologist Bedrich Roth in his pioneering work on idiopathic hypersomnia (IH), a condition that he named and distinguished from narcolepsy.[1] Severe SI refers to the abnormal transitional state between sleep and wake, marked by impaired performance, reduced vigilance, a strong desire to return to sleep, and at times, behavioral abnormalities (including agitation and aggression).[1–3] The duration of SI can vary from minutes to several hours. Severe SI has also been called "sleep drunkenness."[1] Quality-of-life impairment with severe morning SI is often a major problem, adversely affecting timely attendance and performance at school and at work and with family and other interpersonal relationships. *International Classification of Sleep Disorders*, third edition,[2] classifies severe SI as a core feature of IH, describes SI as a potential consequence of delayed sleep-phase syndrome (DSPS), and also as a contributor to the severity and duration of non–rapid eye movement arousal parasomnias. Difficulty with awakening is also common in patients with mood disorders, which merits treatment consideration.[3]

The therapy for severe morning SI remains problematic and challenging. In a recent comprehensive review article by an expert in the field,[3] with the title succinctly stating "Waking up is the hardest thing I do all day," the following pertinent statements were made: "Clinical trials in patients with hypersomnolence disorders have typically not assessed sleep drunkenness,

so an evidence-based approach to its treatment cannot be proposed. Review of clinicaltrials.gov identified only two studies referencing sleep inertia, both testing pharmacological effects of sedative-hypnotics." Anecdotal treatments from case series, beginning with Roth, have included taking direct-release stimulant medication (methylphenidate) at bedtime or 30 minutes before desired morning awakening (namely, involving family member administration, with effort). However, Roth also commented that "some patients do not sleep well after administration of the drugs before going to bed."[1] Sustained-release methylphenidate was not available then. Sporadic therapies have included slow-release melatonin (2 mg) or protriptyline (10–20 mg) at bedtime, along with transdermal and subcutaneous flumazenil, a nicotine patch, and etilefrine, as reviewed.[3] In a series of 46 patients with IH, sodium oxybate improved severe SI in 71%, although discontinuation due to side effects was common.[3] However, this is a costly and inconvenient therapy that, in the United States, would rarely, if ever, be covered by medical insurance. In a review article by other experts on IH 1 year later (2018), no specific therapy for severe SI was proposed,[4] which was also true in the latest review article by another group of experts on IH in 2019.[5] Overall, the proposed therapies for IH target excessive daytime sleepiness and not its commonly associated condition, severe morning SI.

We present a series of 3 consecutive cases of successful therapy for severe morning SI, involving an adolescent female, a young-adult female, and an older-adult male, who responded promptly and in sustained fashion to nightly bedtime long-acting bupropion monotherapy in 2 cases and combined therapy (with long-acting methylphenidate) in 1 case. A fourth patient was intolerant to bupropion-sr (-sustained release). We discuss these findings in the context of a previously reported case series on the successful management of severe morning SI with bedtime long-acting bupropion and/or long-acting methylphenidate, presented in abstracts[6,7] and displayed as posters at 2 Associated Professional Sleep Society meetings by one of the authors (C.H.S.).

METHODS

Patients underwent clinical interviews and examinations and completed comprehensive sleep–wake, medical, and psychiatric questionnaires that also included questions on alcohol, caffeine, and substance use. Patients underwent overnight video-polysomnography (vPSG) and next-day multiple sleep latency test (apart from case 1 with obstructive sleep apnea). Treatments were described in the case reports.

RESULTS

Case 1

A 13-year-old girl had initially presented with her parents to one of the authors (R.P.M.) with the longstanding chief complaint of severe morning SI that greatly interfered with attending school on time during almost every morning, which negatively affected her academic performance, even though she was a capable and highly motivated student. In her mother's words, "My daughter is a hard-working girl who loves school and has high aspirations for her future." She was extremely difficult to arouse, and when she did awaken, she would be very confused, talk nonsensically, and become violent. She had no recollection of these episodes when she later fully awakened. An hour before her scheduled wake-up time, her mother had tried to partially awaken her enough to have her take 10 mg of methylphenidate (prescribed by a previous physician), but with no improvement in the SI when her mother subsequently (1 hour later) tried to get her up for school. The parents affirmed that she regularly practiced excellent sleep hygiene before bedtime. There was no history of daytime somnolence after recovering from each morning SI episode. There was no history of cataplexy, sleep paralysis, or hypnagogic/hypnopompic hallucinations.

Medical history included Ehlers Danlos syndrome and dystonia of her left foot at sleep onset. Psychiatric history included anxiety with obsessive-compulsive features for which she has been taking sertraline, 100 mg daily.

Initial sleep evaluation (with R.P.M.) included an overnight vPSG on 21 October 2016 that confirmed the diagnosis of obstructive sleep apnea, with an apnea-hypopnea index of 7.8 events/h in the supine position. The apnea-hypopnea index overall was 4.2 events/h (despite a previous tonsillectomy and adenoidectomy). Pertinent sleep architecture and other data included the following:

- Total sleep time: 7 hours, 9 minutes
- Stage N1: 3%
- Stage N2: 54%
- Stage N3: 23%
- Stage R: 19%
- Rapid eye movement sleep latency: 167 minutes
- Apnea-hypopnea index: 4.2 events/h
- Arousal index: 18.6 events/h

The vPSG studies on 8 December 2016 and 17 June 2019, while utilizing continuous positive airway pressure (CPAP) therapy at 6 cm water pressure, documented the absence of obstructive sleep apnea; the arousal index was down to 5 events/h. Therefore, she was documented to be successfully treated with nasal CPAP, which took some time for her to tolerate, and for which low-dose bedtime trazodone was effective and then no longer needed. Her CPAP adherence has been consistently excellent. Nevertheless, her severe morning SI persisted for 3 years (with the patient becoming 16 years old) after the initial sleep evaluation and initiation of successful long-term CPAP therapy. The mother then contacted one of the other authors (C.H.S.) after reading a pertinent chapter in his book[8] describing a patient named Sarah with severe morning SI who had been successfully managed with long-acting bedtime stimulant medication. This led to her sleep physician (R.P.M.) conferring with his personally known colleague C.H.S., and bedtime therapy was initiated with bupropion-extended release (xl) 150 mg together with methylphenidate-sr 36 mg, which was found to be the optimal (combined) therapy for controlling her severe morning SI (along with 20 mg methylphenidate taken 1 hour before the alarm would go off, administered by the mother). She was now able to get out of bed in a timely fashion

and arrive at school on time 4 of 5 days of the school week. At a 6-month follow-up, the mother reported ongoing benefit from the same medication regimen, without side effects; her daughter was awakening promptly at her 7:30 AM wake-up time to become ready for her home schooling during the current COVID-19 (coronavirus disease 2019) pandemic.

Case 2

A 29-year-old single woman presented to one of the authors (E.C.G.) for management of IH confirmed by previous nocturnal polysomnography (that ruled out sleep-disordered breathing) and next-day multiple sleep latency test at an out-of-state sleep center, and was managed with Adderall[R] (Teva Pharmaceutical Industries, Ltd., Parsippany, New Jersey) 20 mg in the morning and 10–20 mg later in the day, with partial benefit. She also had a history of DSPS. Over 1 year later, she presented to one of the other authors (C.H.S.) on account of a more than 5-year history of unipolar, nonsuicidal major depression, along with a lifelong history of generalized anxiety disorder; there was a strong family psychiatric history. She had never received any prior psychiatric treatment. The patient also complained of progressively severe morning SI that contributed to her being fired from her job as a food-services manager 18 months previously, and that contributed to diminished effort in looking for another job.

She was prescribed bupropion-xl, 150 mg, at bedtime as therapy for both major depression and severe morning SI. There was immediate and sustained benefit for her severe morning SI, without any concomitant antidepressant benefit. She even commented that "now I know what it is like to feel like a normal person when I wake up in the morning." For her persistent depression, she was offered an additional dose of bupropion-xl to be taken in the morning, but she deferred as she was starting psychotherapy and she also did not know the extent to which her level of depression currently was due to the COVID-19 pandemic and its imposed major social restrictions. The control of her severe morning SI was maintained at a 4-month follow-up. Of note is that her Patient Health Questionnaire-9, a validated screen for the presence and severity of depression in clinical settings, score was 20/27 (borderline severe depression) at baseline and during follow-up visits, which reinforced how the benefit on her severe morning SI from bedtime bupropion-xl was not an antidepressant benefit.

Medical history was positive for infectious mononucleosis, swine flu, and tonsillectomy/adenoidectomy 10 years previously, followed by the onset of IH 2 years later, with confirmatory sleep laboratory testing 1 year afterwards. She could not tolerate methylphenidate, and then generic Adderall[R] therapy was initiated. There was also a more recent-onset history of arthralgias for which an extensive workup for rheumatologic/autoimmune diseases (initiated by E.C.G.) was negative. She had childhood sleepwalking and occasional sleep terrors. There was no history of alcohol or drug abuse. She smokes up to 7 cigarettes daily.

Case 3

A 74-year-old retired married man with longstanding IH had been effectively maintained on a daytime stimulant regimen consisting of methylphenidate-sr, 20 mg 4 times daily, and direct-release methylphenidate 40–50 mg daily in divided doses. He also had a longstanding history of unipolar, nonsuicidal major depression for which bupropion-sr, 300 mg every morning in the morning, had been highly effective. Both of these conditions were managed by one of the authors (C.H.S.). When he complained of progressively severe morning SI, whereby he would not feel fully awake until noon to 1 PM most days, and then start late with his planned daily tasks, he was instructed to take 150 mg bupropion-sr at bedtime and take the other 150-mg dose in the morning. He then experienced prompt resolution of his morning SI, with the daily benefit maintained at a 3-year follow-up.

Case 4

A 60-year-old female with major depression and severe morning SI associated with IH could not tolerate bedtime bupropion-sr, 150 mg, which caused immediate generalized myalgias that resolved within several days of medication cessation.

DISCUSSION

These 4 cases presented with major negative consequences from severe morning SI, ranging from the impact on school attendance and performance (case 1), loss of work and diminished motivation in seeking new employment (cases 2 and 4), and compromised daily activities in retirement (case 3). Their severe morning SI was reversed with bedtime long-acting bupropion therapy, as monotherapy (2 cases) or as combined therapy with long-acting methylphenidate (1 case). There were no medication side effects in 3 cases, and generalized myalgias caused by bupropion-sr in 1 case. Also, all 4 cases had known (multiple) risk factors for SI: sleep disorders (IH in 3 cases, obstructive sleep apnea in 1 case, DSPS in 1 case) and psychiatric disorders (major depression in 3 cases; anxiety with obsessive-compulsive disorder in 1 case). It is notable that in case 1 and case 3, the associated sleep and psychiatric disorders were well controlled, and yet the severe morning SI remained a major daily problem. Also, case 3 had delayed onset, progressively severe, morning SI, without an identified explanation.

The findings just described can be placed within the context of a case series previously reported as abstracts by our Minnesota center.[6,7] In 1996, we reported on successful therapy in 4 of 5 cases treated with bedtime long-acting stimulant therapy.[6] Their data were included in the updated summary data on 22 patients contained in our 2003 abstract.[7] However case 2 in the first abstract[6] merits further description, as her autobiographical story that was published in a book[8] was what prompted the mother of case 1 (16-year-old girl) in the current series to contact the author of the book (C.H.S.), which resulted in the successful collaboration with the treating physician (R.P.M.). As stated in the abstract,[6] a 21-year-old married woman presented to C.H.S. in 1992 with "two main concerns: my children and my job. I don't hear any of my 6 alarm clocks, the phone, my kids, or someone yelling at me. My children can be awake for hours before I wake up. I have been late to work many times because of oversleeping." She eventually had her mother come over every morning to care for her 2 infants until she awakened, usually by noon. Her other sleep history included enuresis until she was 9 years old, childhood sleepwalking, lifelong sleep talking, and lifelong DSPS. Medical history included complex partial seizure disorder, since age 14 years, responding to phenytoin,

which was stopped 4 years previously when she became pregnant. She never resumed phenytoin and had a seizure every 2 months. At our center she underwent 2 consecutive overnight vPSGs, while unmedicated, with a seizure montage and fast paper speeds. No electroencephalographic epileptiform activity was detected. Her total sleep times were 10 hours and 7.8 hours, respectively, with sleep efficiencies of 92–93% (mean sleep latency test, 15.5 minutes [no sleep-onset REM periods]). Treatment with 40 mg methylphenidate-sr and pemoline, 37.5 mg, at bedtime rapidly controlled the severe morning SI. For cost savings, pemoline alone, 150 mg at bedtime, was also fully effective. She awakened promptly every morning needing only 1 alarm clock and got to work on time as a dog groomer.

In 1997, the year after bupropion-sr was released in 1996, she started taking 100–200 mg at bedtime, after switching from her previous stimulant medications (controlled substances), which allowed for refills to be written with each prescription. Then, in 2003, when bupropion-xl was released, she took 150 mg at bedtime, which she found slightly more effective. She quickly noticed that she needed to take this medication just before falling asleep or else her sleep latency would be prolonged for more than 1 hour. She also would take the shorter-lasting bupropion-sr, 100 mg at bedtime, on nights when she did not have to work the following morning, so she could sleep in longer the next day; also, there was no SI on those mornings.

Therefore, severe morning SI responded fully to 2 different bedtime long-acting stimulant medication regimens (methylphenidate, bupropion). However, the bupropion has been much more convenient, as it is not a controlled substance, and so she has received refills lasting 1 year. She recently had her 28th yearly follow-up appointment (with C.H.S.), with full control of her severe morning SI being maintained on the same medication regimen. Also, she has been seizure-free for almost 2 decades. Her autobiographical story[8] is described in the supplemental material.

Data on the treatment of severe morning SI from a series gathered at 1 center over 10 years[7] are summarized in **Table 1**. Overnight vPSGs and next-day multiple sleep latency tests were performed in 21 of 22 patients. The associated psychiatric disorders were usually nonpsychotic mood and anxiety disorders that were in substantial remission. Severe morning SI generally antedated the onset of any associated psychiatric or sleep disorders, was often longstanding (even life-long), and had persisted despite control of any associated disorder. Most patients tended to be long sleepers.

The bedtime long-acting stimulant data in **Table 1** refer to the following medications:

1. Bupropion-sr, n = 5 (100–300 mg at bedtime). n = 1 also took methylphenidate-sr at bedtime.
2. Methylphenidate-sr, n = 12 (20–40 mg). n = 1 also took fluoxetine, 60 mg at bedtime—strictly as a stimulant. Also, n = 1 took 40 mg at 8 AM to induce a full awakening at 9:30 AM (bedtime administration caused a >5-hour sleep latency).
3. Other: (a) methylphenidate direct release, 10 mg at bedtime (16-year-old with DSPS); (b) Modafinil, 200 mg at bedtime (n = 1); (c) tranylcypromine (n = 1), 60 mg at bedtime (prescribed after all other stimulants were ineffective in this nondepressed patient).

Table 1—Data from a series of patients with severe morning SI treated with nightly bedtime sustained-release stimulant medication

	Values
Sex, % female	63.6
Age, mean (SD) [range], years	33 (14.1) [17–50]
Major adverse consequences from SI, n	
Work	12
School	4
Interpersonal	3
Child care	2
Personal medical care responsibilities	1
Associated sleep disorders, % (n/total n)	40.9 (9/22)
OSA, n	3
Narcolepsy, n	3
DSPS, n	2
NREM parasomnia, n	2
PLMD, n	1
Multiple, n	1
Associated psychiatric disorders, % (n/total n)	68.2 (15/22)
SI treatment, substantial/full sustained response, % (n/total n)	86.4 (19/22)
Treatment follow-up, mean (SD) [range], years	2.7 (2.6) [0.5–10]

n = 22. Data from reference 7. DSPS = delayed sleep-phase syndrome; NREM = non–rapid eye movement; OSA = obstructive sleep apnea; PLMD = periodic limb movement disorder; SD = standard deviation; SI = sleep inertia.

Adverse effects were reported in 15.8% (3/22): sleep disruption (mild), n = 1; prolonged sleep latency (described above), n = 1; periodic limb movement disorder aggravation (controlled with gabapentin). (Patients with SI typically are very deep sleepers throughout the night, and so it is not surprising that nocturnal sleep disruption was not reported by any of these 3 cases, nor by the other reported cases.[6,7]).

Bupropion efficacy for severe morning SI

Bupropion is a unique antidepressant (apart from monoamine oxidase inhibitors) insofar as it simultaneously and selectively inhibits reuptake of norepinephrine and dopamine in the central nervous system, which accounts for its activation effects and makes it ideally suited for depressed patients with fatigue, anergia, and/or sleepiness.[9] Furthermore, its lack of affinity for serotonergic, histaminergic, and cholinergic receptors contributes to its lack of producing sedation. It does not suppress rapid eye movement sleep, does not disturb sleep architecture, and does not increase periodic limb movements. Therefore, the pharmacologic activation effect and lack of sedation effect, along with minimal propensity for disturbing sleep, may be the basis for the efficacy of long-acting bupropion taken at bedtime to control severe morning SI. However, the mechanism of therapeutic action for SI remains to be established. (It should be noted that an initially treatment-resistant patient with SI listed in **Table 1**

responded selectively to bedtime tranylcypromine, a monoamine oxidase inhibitor sharing the same norepinephrine and dopamine reuptake inhibition property as bupropion.) Bupropion generally carries a favorable side-effect profile, with no cardiovascular effects,[10] lack of weight gain, and lack of sexual dysfunction. It can sometimes cause or increase irritability and anger, and cause or increase paranoia because of its dopaminergic property. Seizures are a risk at high doses, but none of the patients reported herein was taking a dose higher than 300 mg. Patient 4 in our series had an unusual reaction with generalized myalgias that quickly subsided with bupropion discontinuation.

CONCLUSIONS

The beneficial effects of the treatments described herein were not antidepressant responses, as benefit was often achieved after the first night, or after the first few nights of therapy, in contrast to antidepressant therapy when the benefit emerges after 1–3 weeks from the start of therapy. Also, most of these patients were not actively depressed at the start of treatment. Our findings confirm and extend those of Roth et al[1] from nearly 50 years ago on the efficacy of bedtime stimulant therapy for severe morning SI, with the current-day benefit of having long-acting methylphenidate available, along with long-acting bupropion. Our findings are also consistent with prior findings that severe morning SI can often be found with hypersomnia disorders and with psychiatric disorders,[11,12] although the basis for these associations needs to be clarified, as recently discussed.[3–5] Nevertheless, SI requires separate treatment from its associated disorders, apart from some cases of comorbid depression, for which bedtime bupropion-xl can exert dual benefit, as seen with case 3.

Finally, our findings should encourage further clinical use of bedtime long-acting bupropion and/or long-acting methylphenidate as therapy for severe morning SI. Also, systematic research in this area is encouraged.

ABBREVIATIONS

CPAP, continuous positive airway pressure
DSPS, delayed sleep phase syndrome
SI, sleep inertia
sr, sustained release
vPSG, video-polysomnography
xl, extended release

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the institutional affiliations listed above. C.H.S. was a consultant for Axovant Sciences until December 31, 2020, outside the submitted work. The other authors report no conflicts of interest.