https://doi.org/10.5664/jcsm.8738

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Advance taper of antidepressants prior to multiple sleep latency testing increases the number of sleep-onset rapid eye movement periods and reduces mean sleep latency

Bhanu Prakash Kolla, MD, FRCPsych[1,2]; Marjan Jahani Kondori, MD[3]; Michael H. Silber MBChB[2]; Hala Samman, MD[2]; Swati Dhankikar, MD[2]; Meghna P. Mansukhani, MD[2,3]

[1]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota; [2]Center for Sleep Medicine, Mayo Clinic, Rochester, Minnesota; [3]Department of Family Medicine, Mayo Clinic, Rochester, Minnesota

Study Objectives: Patients presenting with excessive sleepiness are frequently using antidepressant medication(s). While practice parameters recommend discontinuation of antidepressants prior to multiple sleep latency testing (MSLT), data examining the impact of tapering these medications on MSLT results are limited.

Methods: Adult patients who underwent MSLT at Mayo Clinic Rochester, Minnesota, between 2014 and 2018 were included. Clinical and demographic characteristics, medications, including use of rapid eye movement–suppressing antidepressants (REMS-ADs) at assessment and during testing, actigraphy, and polysomnography data were manually abstracted. The difference in number of sleep-onset rapid eye movement periods (SOREMs), proportion with ≥2 SOREMs, and mean sleep latency in patients who were using REMS-ADs and discontinued prior to testing versus those who remained on REMS-ADs were examined. At our center, all antidepressants are discontinued 2 weeks prior to MSLT, wherever feasible; fluoxetine is stopped 6 weeks prior. Regression analyses accounting for demographic, clinical, and other medication-related confounders were performed.

Results: A total of 502 patients (age = 38.18 ± 15.90 years; 67% female) underwent MSLT; 178 (35%) were taking REMS-ADs at the time of assessment. REMS-AD was discontinued prior to MSLT in 121/178 (70%) patients. Patients whose REMS-AD was discontinued prior to MSLT were more likely to have ≥2 SOREMs (odds ratio: 12.20; 95% confidence interval: 1.60–92.94) compared with patients on REMS-ADs at MSLT. They also had shorter mean sleep latency (8.77 ± 0.46 vs 10.21 ± 0.28 minutes; $P > .009$) and higher odds of having ≥2 SOREMs (odds ratio: 2.22; 95% confidence interval: 1.23–3.98) compared with patients not taking REMS-ADs at initial assessment. These differences persisted after regression analyses accounting for confounders.

Conclusions: Patients who taper off REMS-ADs prior to MSLT are more likely to demonstrate ≥2 SOREMs and have a shorter mean sleep latency. Pending further prospective investigations, clinicians should preferably withdraw REMS-ADs before MSLT. If this is not done, the test interpretation should include a statement regarding the potential effect of the drugs on the results.

Keywords: multiple sleep latency testing, antidepressants, REM suppression, sleep latency

Citation: Kolla BP, Jahani Kondori MJ, Silber MH, Samman H, Dhankikar S, Mansukhani MP. Advance taper of antidepressants prior to multiple sleep latency testing increases the number of sleep-onset rapid eye movement periods and reduces mean sleep latency. *J Clin Sleep Med*. 2020;16(11):1921–1927.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Current practice parameters recommend that REM-suppressant antidepressant medications should ideally be tapered 2 weeks prior to multiple sleep latency testing. However, empirical evidence supporting these recommendations is limited.

Study Impact: Patients who taper off REM-suppressant antidepressant medications prior to multiple sleep latency testing are more likely to demonstrate ≥2 sleep-onset REM episodes and have a shorter multiple sleep latency. Pending further prospective investigations, clinicians should preferably withdraw these medications prior to multiple sleep latency testing.

INTRODUCTION

Multiple sleep latency testing (MSLT) involves providing patients with 4–5 nap opportunities at 2-hour intervals and measures their propensity to fall asleep.[1] It is designed to objectively quantify sleepiness under standardized conditions and detect the presence of abnormal sleep-onset rapid eye movement (REM) episodes (SOREMs) occurring within 15 minutes of sleep onset.[2] The presence of ≥2 SOREMs is considered abnormal and, in conjunction with a mean sleep latency (MSL) of ≤8 minutes on MSLT, is indicative of a diagnosis of narcolepsy.[3] In clinical practice, MSLT is the mainstay in evaluating pathological sleepiness and diagnosing central disorders of hypersomnolence such as narcolepsy. In order to obtain valid results, the MSLT must be performed under standardized conditions. The American Academy of Sleep Medicine practice parameters have clearly laid out recommendations for the conduct of MSLT.[2] These parameters indicate that, ideally, REM sleep–suppressing medications should be discontinued 2 weeks prior to testing in order to minimize

false-negative test results due to these medications potentially suppressing SOREMs.

Major depression and other depressive disorders are common in individuals from both community and clinic samples who complain of excessive sleepiness.[4–8] Conversely, depressive symptoms are frequently reported by patients with narcolepsy.[9,10] Therefore, it is common for individuals to be using REM-suppressant antidepressants (REMS-ADs) at the time of initial assessment for excessive sleepiness. Evaluation with MSLT ideally requires a period of at least 2 weeks without the use of these medications prior to the test. This decision is fraught, as discontinuing antidepressant medications can result in relapse of depression and requires close collaboration between sleep and mental health providers. The evidence examining the utility of tapering and discontinuing REMS-ADs prior to MSLT on the results of the test is extremely limited.

A study assessing the correlates to SOREMs did not find an association between the use of REMS-ADs and having ≥1 or ≥2 SOREMs.[11] This study examined a community sample who underwent MSLT under nonstandardized conditions. A more recent study examining a clinical sample found that patients using REM sleep suppressants at the time of the MSLT were less likely to have ≥2 SOREMs.[12] This investigation was limited by patients self-reporting their use of REM sleep suppressants at the time of polysomnography (PSG), lack of information about a standard taper prior to testing, and no objective verification of absence of these drugs at the time of the test. In addition, this study did not compare outcomes in patients who were on REMS-ADs at the time of the initial assessment and discontinued them prior to testing versus those who continued taking REMS-ADs at the time of the MSLT.

In the current study, we evaluated a sample of adults presenting to a tertiary-level sleep center for an evaluation of excessive sleepiness. The main aim of this study was to examine the impact of tapering REMS-ADs well in advance of MSLT on the number of SOREMs detected and the MSL on this test. We were able to objectively verify absence of these drugs in a significant proportion of patients due to standard use of urine drug testing at the time of the MSLT. We categorized patients into those who were not on REMS-ADs at the time of the initial assessment and subsequent MSLT, those who tapered and discontinued REMS-ADs in advance of MSLT, and those who remained on these medications. We accounted for potential confounders, including other clinical and demographic characteristics, other medications, data from wrist actigraphy, and PSG performed prior to MSLT.

METHODS

Sample and data

This was a retrospective study. Data from all adult patients who underwent MSLT at the Center for Sleep Medicine, Mayo Clinic, Rochester, Minnesota, between 2014 and 2018 and provided research authorization were included in the analyses. This study had the requisite Institutional Review Board approval (IRB no.: 18-006798).

Demographic details, information regarding clinical characteristics including Epworth sleepiness scale scores, self-reported sleep duration including naps, documentation of shift work, history of depression, presence of cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, and medication use at the baseline visit were manually abstracted from the clinical record. Medications were further categorized into antidepressants that were not REM suppressing (ie, non-REMS-ADs; trazodone, nefazodone, mirtazapine and bupropion),[11,13] REMS-ADs (all remaining antidepressants), benzodiazepines and non–benzodiazepine benzodiazepine receptor agonists (nBBRAs), and "other" sedating medications, stimulants, or wakefulness-promoting medications. Average total sleep time, time in bed, and sleep efficiency were extracted from actigraphy reports. Total sleep time, sleep-onset latency, sleep efficiency, arousal index, apnea-hypopnea index, and initial REM latency were obtained from the PSG report. The PSG was performed on the night prior to MSLT. Sleep latencies for each nap, MSL, and the number of SOREMs (defined as REM onset within 15 minutes of sleep onset) were abstracted from the MSLT. If patients had >1 MSLT performed during the time frame of the study, only data from the first test were analyzed.

MSLT protocol

In our center, all patients are evaluated by a sleep medicine provider prior to any sleep-related testing. Patients undergoing MSLT are advised to discontinue all antidepressants, stimulants, and other wakefulness-promoting agents, benzodiazepines, nBBRAs, and other sedative/hypnotic medications at least 2 weeks prior to testing. In the case of fluoxetine, given its long half-life, patients are asked to taper and discontinue the medication at least 6 weeks prior to testing. Exceptions are made on a case-by-case basis contingent on the patient and his or her mental health provider's comfort with the taper, psychiatric stability, and expediency of testing. In addition, patients undergo 1- to 2-week wrist actigraphy with sleep logs to monitor sleep times and daily routines leading up to MSLT. Patients who are determined to have insufficient sleep based on history and/or actigraphy do not undergo further testing. Positive airway pressure therapy at prescribed settings is utilized during MSLT, if applicable. Urine drug testing examining for both prescription and illicit drugs is performed on the day of the MSLT.

Statistical analyses

Patients were categorized into 3 groups: (1) not using REMS-ADs at the time of the initial assessment, (2) using REMS-ADs at the time of the initial assessment but the REMS-AD was discontinued prior to MSLT, and (3) using REMS-ADs at the time of the initial assessment and continued on REMS-ADs at MSLT. Group differences in demographic and clinical characteristics, PSG, and MSLT outcomes were assessed with either analysis of variance or chi-square analysis, with Bonferroni post hoc tests accounting for multiple testing, depending on the nature of data. Logistic regression analyses were used to examine the associations between MSL (treated as a continuous variable) and ≥2 SOREMs (treated as a dichotomous variable), which were treated as the dependent variables, and potential confounders. Regression models were run progressively to adjust for (1) demographic characteristics including age, sex, and body mass index; (2) clinical factors including a history of

Table 1—Baseline characteristics.

Variable (Total Sample, n = 498)	Not Using a REMS-AD at Assessment (n = 324, 65%)	REMS-AD Continued at MSLT (n = 53, 11%)	REMS-AD Tapered Prior to MSLT (n = 121, 24%)	*P*
Demographic characteristics				
Age (mean ± SE), years	38.29 ± 0.88	38.94 ± 2.19	37.15 ± 1.45	.73
Sex, % female	60.8	81.13	77.69	.0002*
BMI, kg/m^2	27.34 ± 0.34	28.31 ± 0.85	29.05 ± 0.57	.03
Clinical characteristics				
ESS (mean ± SE)	13.88 ± 0.32	14.70 ± 0.77	15.33 ± 0.52	.06
Self-reported sleep duration (mean ± SE), hours	8.69 ± 0.12	8.35 ± 0.31	9.13 ± 0.20	.07
Shift work, %	6.48	5.77	6.84	.77
Cataplexy, %	7.10	9.43	5.79	.69
Hypnogogic hallucinations, %	8.64	9.43	14.05	.26
Hypnopompic hallucinations, %	6.48	5.66	9.09	.59
Sleep paralysis, %	14.20	13.21	16.53	.86
Insomnia, %	20.06	28.30	12.40	.03
Depression, %	21.30	71.70	60.50	<.0001*
Non–REMS-AD, %	21.98	45.28	38.33	<.0001*
Benzodiazepines, %	5.86	16.98	9.92	.03
nBBRAs, %	4.63	5.66	4.13	.91
Actigraphy data (n = 419) (mean ± SE)				
Total sleep time, hours	7.35 ± 0.07	7.63 ± 0.17	7.56 ± 0.11	.14
Time in bed, hours	8.60 ± 0.08	8.99 ± 0.19	8.89 ± 0.13	.05
Sleep efficiency, %	84.64 ± 0.45	84.53 ± 1.08	84.32 ± 0.73	.93
PSG Data (n = 482) (mean ± SE)				
Total sleep time, minutes	426.95 ± 5.22	425.76 ± 12.79	429.10 ± 8.45	.97
Sleep efficiency, %	82.35 ± 0.68	81.18 ± 1.66	83.76 ± 1.10	.37
Sleep-onset latency, minutes	19.68 ± 1.30	34.90 ± 3.18	18.54 ± 2.10	<.001#
Arousal index, events/h	16.35 ± 0.61	18.84 ± 1.49	18.45 ± 0.99	.09
AHI, events/h	1.66 ± 0.23	1.75 ± 0.55	2.37 ± 0.36	.25
Initial REM latency, minutes	100.61 ± 4.70	183.64 ± 11.52	91.48 ± 7.61	<.001#

AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth sleepiness scale; MSLT = multiple sleep latency testing; nBBRA, non–benzodiazepine benzodiazepine receptor agonist; PSG = polysomnography; REM = rapid eye movement; REMS-AD = rapid eye movement–suppressing antidepressant. *Indicates a significant difference between the three groups, after accounting for multiple testing. #Indicates a significant difference between those on REMS-ADs at MSLT and the other 2 groups, after accounting for multiple testing.

depression, shift work, benzodiazepine, nBBRA, and non–REMS-AD use at assessment; and (3) total sleep time on actigraphy and total sleep time and arousal index on PSG. These variables were chosen a priori for inclusion in analyses as factors that could potentially affect the outcomes being assessed.[14] All comparisons were 2-tailed. Analyses were performed utilizing JMP software (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics

The total sample consisted of 498 patients (mean age: 38.19 ± 15.10 years), a majority of whom were female (67%). One hundred seventy-four (174/498; 34.6%) patients were using REM-ADs at the time of assessment and 69.5% (121/174) of these tapered and discontinued these medications prior to testing. Actigraphy was performed in 419 (83.4%) and PSG in 482 (96%) patients prior to MSLT. The mean duration between initial assessment and MSLT for the entire sample was 12.28 ± 3.49 days. For patients using REMS-ADs at the initial assessment, the mean duration was 27.34 ± 4.44 days.

Baseline demographics, clinical characteristics, medications, actigraphy, and PSG data for the 3 categories are detailed in **Table 1**. Patients who were using REMS-ADs, either tapered prior to MSLT or not, were more likely to be female, report a history of depression, and on a non–REMS-AD at the time of assessment compared with patients who were not taking a REMS-AD at initial assessment. Those who were taking a REMS-AD at the time of MSLT were more likely

Table 2—Differences in MSLT outcomes.

Variable	Not Using a REMS-AD at Assessment (n = 324)	REMS-AD Continued at MSLT (n = 53)	REMS-AD Tapered Prior to MSLT (n = 121)
Mean sleep latency, minutes	10.21 ± 0.28	9.20 ± 0.70	8.78 ± 0.46*
Mean number of SOREMs	0.36 ± 0.06	0.13 ± 0.15	0.65 ± 0.10#
Patients with ≥2 SOREMs, n (%)	31 (9.57)	1 (1.89)	23 (19.1)#
Patients meeting criteria for narcolepsy, n (%)	19 (5.86)	1 (1.89)	16 (13.22)#

MSLT = multiple sleep latency testing; REMS-AD = rapid eye movement suppressing antidepressant; SOREM = sleep-onset rapid eye movement episode. *P value < .009 compared with mean sleep latency for patients not on a REMS-AD at assessment. #P value < .05 compared with mean number of SOREMS, % with ≥2 SOREMs, and % meeting criteria for narcolepsy (mean sleep latency ≤8 minutes and ≥2 SOREMs) on MSLT for patients not on a REMS-AD at assessment and those who continued on REMS-AD at the time of MSLT.

Table 3—Odds of ≥2 SOREMS on MSLT in patients who discontinued REMS-AD prior to MSLT.

	Unadjusted Model		Model 1		Model 2		Model 3	
	Not Using a REMS-AD	Using a REMS-AD During MSLT	Not Using a REMS-AD	Using a REMS-AD During MSLT	Not Using a REMS-AD	Using a REMS-AD During MSLT	Not Using a REMS-AD	Using a REMS-AD During MSLT
REMS-AD discontinued prior to MSLT	2.21 (1.23–3.98)	12.20 (1.60–92.94)	2.45 (1.32–4.52)	12.08 (1.57–92.46)	3.33 (1.69–6.56)	10.75 (1.39–83.14)	3.16 (1.49–6.68)	8.11 (1.01–65.27)

Values are ORs (95% CIs). Model 1 adjusted for age, sex and BMI; model 2 additionally adjusted for depression, shift work, and benzodiazepine, nBBRA, and non–REM-suppressant antidepressant use; model 3 additionally adjusted for total sleep time on actigraphy and total sleep time and arousal index on PSG. BMI = body mass index; CI = confidence interval; MSLT = multiple sleep latency testing; nBBRA = nBBRA, non–benzodiazepine benzodiazepine receptor agonist; OR = odds ratio; PSG, polysomnography; SOREM = sleep-onset rapid eye movement episode; REM rapid eye movement; REMS-AD = rapid eye movement–suppressing antidepressant.

to have prolonged sleep-onset latency and initial REM latency on PSG compared with the other 2 groups. There were no differences in rates of actigraphy, PSG, and urine drug testing among the 3 groups. Additional data are shown in the **Supplemental Material**.

Urine drug testing results

Urine drug testing was performed in 396 (79%) of the patients. Two patients who were instructed to discontinue REMS-ADs tested positive for these substances (one for citalopram and another for fluoxetine) on urine drug testing. For the purposes of the current analyses, they were categorized as not having tapered off the REMS-AD. All patients who were using benzodiazepines, nBBRAs, other sedating medications, stimulants, and non–REMS-ADs were advised to discontinue these medications prior to testing. However, 4 patients tested positive for benzodiazepines and 4 patients tested positive for bupropion; additional sensitivity analyses were performed after excluding these patients from the dataset. These sensitivity analyses did not reveal any changes to the results.

Impact of remaining on REMS-ADs on MSLT findings

Patients who tapered off REMS-ADs prior to MSLT had a shorter MSL than patients who were not using REMS-ADs at initial assessment (8.77 ± 0.46 vs 10.21 ± 0.28; $P < 0.009$). The difference in the MSL between patients who tapered off REM-ADs at MSLT and those who remained on these medications was not significant, nor was the difference between patients who remained on REM-ADs at MSLT and those not using REMS-ADs at initial assessment (Table 2).

Patients who tapered off REMS-ADs prior to MSLT had a greater number of SOREMs and were more likely to have ≥2 SOREMs on MSLT compared with both those who remained on REMS-ADs at MSLT and those not on REMS-ADs at initial assessment (Table 2).

After regression analyses controlling for age, sex, body mass index, depression, shift work, benzodiazepine, nBBRA, and non–REMS-AD use at the time of assessment, total sleep time on actigraphy, and total sleep time and arousal index on PSG, patients who tapered off REMS-ADs prior to MSLT were still more likely to have ≥2 SOREMs on MSLT compared with the other 2 groups (Table 3). Similarly, after accounting for these confounders, patients who tapered off REM-ADs prior to MSLT were more likely to have a shorter MSL than those who were not on REM-ADs at the time of the initial assessment.

DISCUSSION

Our study compared MSLT outcomes in patients who presented for an evaluation of excessive sleepiness, a majority of whom underwent a standard taper of REMS-ADs at least 2 weeks in advance of the MSLT. The results revealed that those who tapered REMS-ADs prior to MSLT were more likely to demonstrate SOREMs compared with those who continued or were not using these medications. In addition,

they had a shorter MSL compared with patients who were not using REMS-ADs at the time of the initial assessment. These results indicate the value in planning and executing a taper of these medications prior to MSLT in order to obtain valid and accurate results. The findings provide empirical evidence supporting the American Academy of Sleep Medicine practice parameters, which recommend such a taper when feasible prior to conducting a resource- and time-intensive diagnostic test.

MSLT was developed to detect quantitative differences in sleep tendencies between individuals with narcolepsy and controls. It is currently the gold-standard test to measure objective sleepiness and to diagnose narcolepsy. The test is expensive, requires extensive resources, and entails significant commitment from the patient in terms of his or her time. Therefore, where possible, the testing should be performed under ideal circumstances to avoid erroneous results. Appropriate preparation of patients for testing requires obtaining adequate total sleep time, eliminating causes of nighttime sleep disruption and other factors that might impede the occurrence of SOREMs. While the initial guidelines on the conduct of the test and current practice parameters recommend discontinuation of REMS-ADs prior to testing, evidence on the utility of discontinuing these medications prior to testing is scant.[15]

A previous study examining the factors influencing SOREMs on MSLT in a community-based sample reported that SOREMs were common, especially among men, when the testing was conducted under nonstandardized conditions.[11] In this study, SOREMs were associated with other clinical features commonly seen in narcolepsy, shorter sleep duration the day prior to testing, and use of non–REMS-ADs; the use of REMS-ADs did not influence the number of SOREMs. A subsequent study of a larger cohort that included the previous sample did not find an association between SOREMs and REMS-ADs.[16] A more recent study examined a clinical sample and utilized data obtained from a patient self-reported questionnaire administered on the night of the PSG prior to MSLT.[12] Information with regard to medication use and discontinuation and sleep duration was obtained from this questionnaire. Objective verification of absence of medication during the MSLT through urine drug testing was not available. This study found that, in patients over the age of 60 years, those reporting the use of REM-suppressant medications and women were less likely to demonstrate ≥2 SOREMs. The impact of tapering these medications for the purposes of testing was not clear. In contrast, our study included a sample of patients seeking care for a complaint of excessive sleepiness and detailed information regarding current medication use and documentation of a planned taper well in advance of scheduled MSLT was available. Medication discontinuation was verified by reviewing urine drug-testing results conducted on the day of the MSLT. Additionally, objective estimates of sleep duration preceding MSLT were available from actigraphy and PSG.

As expected, our study demonstrated that patients who tapered off REMS-ADs prior to MSLT were more likely to exhibit SOREMs on MSLT. A majority of antidepressants have been shown to suppress REM sleep on nocturnal PSG and remaining on these medications during MSLT could conceivably result in a reduction in the number of SOREMs.[13,17] A potential rebound in the amount of REM sleep obtained can occur following the discontinuation of REMS-ADs.[18–20] This appears to settle in about 2 weeks following discontinuation of tricyclic antidepressants.[18,21] Data regarding the time frame following which the REM rebound secondary to selective serotonin reuptake inhibitor and other newer antidepressant discontinuation resolves are sparse.[22] Therefore, the possibility that the increase in the number of SOREMs was secondary to REM rebound persisting for weeks following REMS-AD discontinuation exists but is likely remote. Patients who tapered off REMS-ADs prior to MSLT also had a shorter MSL than patients who were not using REMS-ADs at initial assessment. Discontinuing these medications prior to MSLT can improve the chances of detecting SOREMs and short MSLs, thus aiding in making an accurate diagnosis.

A previous case-control study showed that a substantial proportion of patients with narcolepsy had comorbid major depression, a majority of whom were diagnosed with depression prior to receiving a diagnosis of narcolepsy.[23,24] Therefore, it is likely that patients with comorbid depression and undiagnosed narcolepsy would already be using a REMS-AD when they present for an evaluation of excessive sleepiness. In our sample of treatment-seeking patients with excessive sleepiness, a substantial proportion reported a history of depression and were taking antidepressants at the time of assessment. Prior epidemiologic studies have also shown considerable overlap between self-reported excessive sleepiness and depression.[4–6] Across the 3 groups of patients in our study, self-reported sleepiness measured by the Epworth sleepiness scale and most other clinical factors, including supportive features for a diagnosis of narcolepsy, were similar at baseline, suggesting that patients across the 3 groups had similar clinical presentation at the time of the initial assessment.

There were no differences in actigraphy-derived data between the 3 groups, indicating that tapering REMS-ADs did not result in significant sleep disruption or changes to total sleep time leading up to the test. Although overall data are mixed, there are reports that antidepressants may have activating effects and some prior studies have shown that these medications can result in prolonged sleep-onset latencies.[25,26] The use of REMS-ADs appeared to result in a suppression of REM sleep and reduced propensity to fall asleep quickly on PSG in our study, in keeping with the results from prior studies.[13,17,25,26]

At our center, patients who present with excessive sleepiness undergo thorough clinical evaluation. In accordance with the American Academy of Sleep Medicine practice parameters, patients considered to be at risk of central disorders of hypersomnolence undergo further testing including MSLT. In our sample, a total of 7.2% met criteria for narcolepsy and 35.1% met criteria for idiopathic hypersomnia based on the MSLT findings. The relatively large proportion of patients who do not meet MSLT criteria

for a diagnosis of narcolepsy/idiopathic hypersomnia likely reflects the referral nature of our practice, which includes many misdiagnosed patients refractory to stimulant therapy who actually have other diagnoses such as chronic fatigue syndrome.

Our study should be considered in light of some limitations. While it is standard practice at our center to taper and discontinue REMS-ADs at least 2 weeks prior to testing per American Academy of Sleep Medicine practice parameters, it is possible that, in some cases, the patients might have discontinued the medication much closer to MSLT and thus an increased number of SOREMs due to a withdrawal phenomenon cannot be completely ruled out. Additionally, while it is standard practice at our center to perform urine drug screening that also tests for prescription drug use, not all patients had this done and some may have remained on their medications despite being advised to discontinue them. It seems unlikely that this would affect the overall results as the majority did have urine drug testing performed and there were no differences in the rates of testing between the 3 groups. Although we accounted for a history of depression in our analyses, the severity of current depressive symptoms was not available and there is a possibility that the increase in number of SOREMs was secondary to untreated depression at the time of MSLT. However, in routine clinical practice it would be unlikely that patients with moderate to severe depression with active depressive symptoms would have their medication(s) discontinued.

CONCLUSIONS

A history of depression and the use of antidepressants are extremely common in clinical samples presenting for an assessment of excessive sleepiness. Tapering and discontinuation of REMS-ADs require advance planning and coordination of care and are not uniformly performed prior to MSLT testing. Our data suggest that those who tapered off REMS-ADs prior to MSLT are significantly more likely to have ≥2 SOREMs and also demonstrate a shorter MSL. Pending future prospective large-scale studies, wherever possible, clinicians should attempt to discontinue these medications prior to testing in order to avoid false-negative test results and reduce the chances of missing a diagnosis of narcolepsy. When this is not feasible, the interpretation of the test should clearly state that the tests were performed while the patient remained on REMS-ADs to allow other providers to contextualize the results and plan appropriate management.

ABBREVIATIONS

MSL, mean sleep latency
MSLT, multiple sleep latency testing
nBBRA, non–benzodiazepine benzodiazepine receptor agonist
REM, rapid eye movement
REMS-AD, rapid eye movement–suppressant antidepressant
SOREM, sleep-onset rapid eye movement episode

REFERENCES

1. Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr Clin Neurophysiol.* 1978; 45(5):621–627.
2. Littner MR, Kushida C, Wise M, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep*. 2005;28(1):113–121.
3. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
4. Kolla BP, He JP, Mansukhani MP, Frye MA, Merikangas K. Excessive sleepiness and associated symptoms in the U.S. adult population: prevalence, correlates, and comorbidity. *Sleep Health*. 2020;6(1):79–87.
5. Ohayon MM. Determining the level of sleepiness in the American population and its correlates. *J Psychiatr Res.* 2012;46(4):422–427.
6. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *JAMA*. 1989;262(11): 1479–1484.
7. Mosko S, Zetin M, Glen S, et al. Self-reported depressive symptomatology, mood ratings, and treatment outcome in sleep disorders patients. *J Clin Psychol.* 1989;45(1):51–60.
8. Lopez R, Barateau L, Evangelista E, Dauvilliers Y. Depression and hypersomnia: a complex association. *Sleep Med Clin.* 2017;12(3):395–405.
9. Dauvilliers Y, Paquereau J, Bastuji H, Drouot X, Weil JS, Viot-Blanc V. Psychological health in central hypersomnias: the French Harmony study. *J Neurol Neurosurg Psychiatry.* 2009;80(6):636–641.
10. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. *J Sleep Res.* 2001;10(1):75–81.
11. Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, Young T. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. *Brain*. 2006;129(6):1609–1623.
12. Cairns A, Trotti LM, Bogan R. Demographic and nap-related variance of the MSLT: results from 2,498 suspected hypersomnia patients: clinical MSLT variance. *Sleep Med.* 2019;55:115–123.
13. Doghramji K, Jangro WC. Adverse effects of psychotropic medications on sleep. *Psychiatr Clin North Am.* 2016;39(3):487–502.
14. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies. guidance for authors from editors of respiratory, sleep, and critical care journals. *Ann Am Thorac Soc.* 2019;16(1): 22–28.
15. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep*. 1986;9(4):519–524.
16. Goldbart A, Peppard P, Finn L, Ruoff CM, Barnet J, Young T, Mignot E. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. *Sleep*. 2014;37(6):1043–1051.
17. Zhang B, Hao Y, Jia F, et al. Sertraline and periodic limb movements during sleep: an 8-week open-label study in depressed patients with insomnia. *Sleep Med.* 2013;14(12):1405–1412.
18. Dunleavy DLF, Brezinova V, Oswald I, Maclean AW, Tinker M. Changes during weeks in effects of tricyclic drugs on the human sleeping brain. *Br J Psychiatry.* 1972;120(559):663–672.
19. Silvestri R, Pace-Schott EF, Gersh T, Stickgold R, Salzman C, Hobson JA. Effects of fluvoxamine and paroxetine on sleep structure in normal subjects: a home-based Nightcap evaluation during drug administration and withdrawal. *J Clin Psychiatry.* 2001;62(8):642–652.
20. Gillin JC, Wyatt RJ, Fram D, Snyder F. The relationship between changes in REM sleep and clinical improvement in depressed patients treated with amitriptyline. *Psychopharmacology (Berl).* 1978;59(3):267–272.
21. Lauer CJ, Pollmächer T. On the issue of drug washout prior to polysomnographic studies in depressed patients. *Neuropsychopharmacology.* 1992;6(1):11-16.

22. van Bemmel AL, van den Hoofdakker RH, Beersma DGM, Bouhuys AL. Changes in sleep polygraphic variables and clinical state in depressed patients during treatment with citalopram. *Psychopharmacology (Berl)*. 1993;113(2): 225–230.
23. Lee M-J, Lee S-Y, Yuan S-S, et al. Comorbidity of narcolepsy and depressive disorders: a nationwide population-based study in Taiwan. *Sleep Med.* 2017;39:95–100.
24. Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. *Sleep Med.* 2018;43:14–18.
25. Beasley CM Jr, Sayler ME, Weiss AM, Potvin JH. Fluoxetine: activating and sedating effects at multiple fixed doses. *J Clin Psychopharmacol.* 1992;12(5):328–333.
26. Vasar V, Appelberg B, Rimón R, Selvaratnam J. The effect of fluoxetine on sleep: a longitudinal, double-blind polysomnographic study of healthy volunteers. *Int Clin Psychopharmacol.* 1994;9(3):203–206.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December 24, 2019
Submitted in final revised form August 5, 2020
Accepted for publication August 5, 2020
Address correspondence to: Bhanu Prakash Kolla, MD, FRCPsych, Mayo Clinic, 200 First Street SW, Rochester, MN 55905; Tel: (507) 266-1066; Fax: (507) 266-6772; Email: kolla.bhanuprakash@mayo.edu

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.