pii: jc-00264-16 http://dx.doi.org/10.5664/jcsm.6294

JCSM
Journal of Clinical Sleep Medicine

SLEEP MEDICINE PEARLS

An Unexpected Polysomnogram Finding

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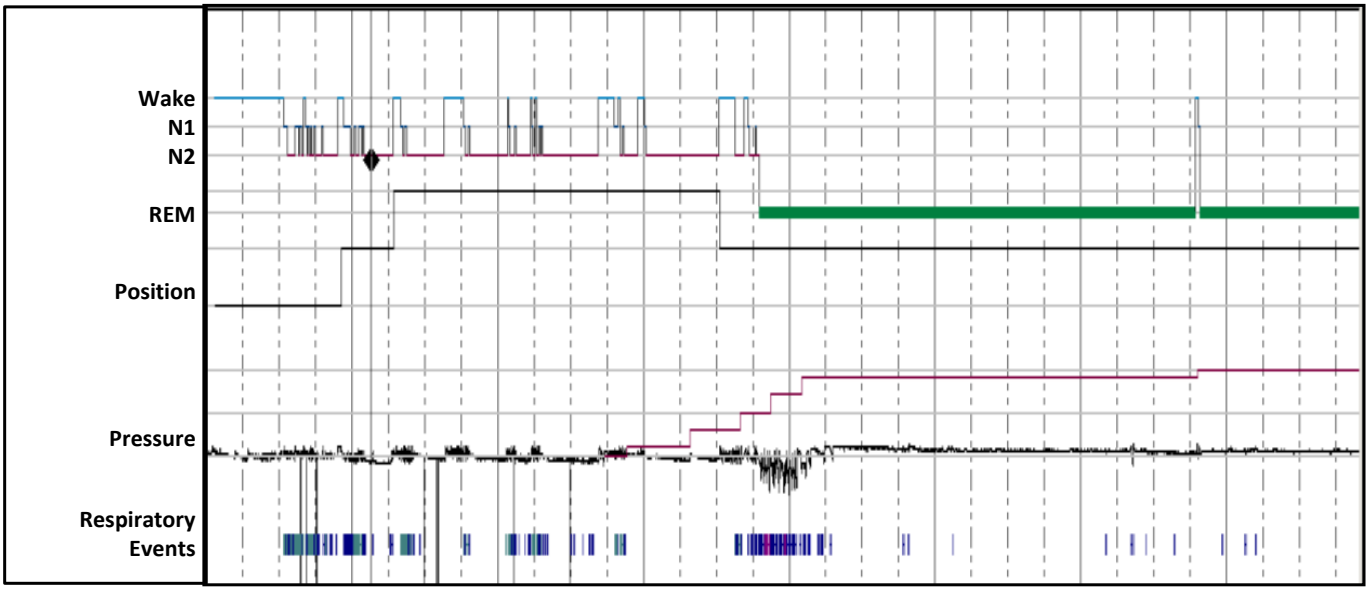
A 56-year-old obese female with depression was referred for evaluation of snoring, witnessed apneas, and daytime fatigue. Prescribed medications included bupropion and sertraline.

Split-night polysomnography was performed. The diagnostic portion revealed total sleep time of 112 minutes, the absence of REM sleep, and an apnea-hypopnea index (AHI) of 54 events per hour. Continuous positive airway pressure (PAP) titration was then initiated starting at 5 cm H_2O. At a pressure of approximately 12 cm H_2O, the patient entered a long uninterrupted period of REM sleep lasting 140 minutes (**Figure 1**). Titration REM latency was 48 minutes, with REM occupying 242 minutes of the 292 minutes of titration sleep time. REM represented 83% of titration sleep time and 60% of total study sleep time. PAP was further titrated to an optimal pressure of 14 cm H_2O.

QUESTION: What are the potential etiologies of increased REM sleep in this patient?

Figure 1



ANSWER: REM rebound related to PAP initiation, use of REM-prolonging antidepressant, and withdrawal of REM-suppressing antidepressant.

DISCUSSION

REM sleep is ubiquitous among mammals, and its preservation across species is a testament to its biological importance. REM sleep is defined by low-amplitude, mixed-frequency EEG activity, rapid eye movements, and skeletal muscle atonia sparing the diaphragm and ocular muscles. In healthy adults, REM sleep comprises 15% to 25% of total sleep time, occurring in 90-120 minute cycles that typically increase in duration with each REM period. Many clinical factors can alter REM onset and/or duration (**Table 1**). "REM rebound" is a descriptive term for abrupt increases in REM activity (either increased duration or frequency of REM cycling) that may be observed in a variety of clinical scenarios including sleep deprivation, PAP initiation, and withdrawal of REM-suppressing drugs.

A proposed working definition of significant REM rebound is a 20% increase in REM duration (in minutes) between pressure titration and diagnostic PSG, as a percentage of the diagnostic PSG REM duration.[1] This working definition was proposed by Brillante et al., based on evaluation of paired diagnostic PSG followed by CPAP titration studies (each performed on a separate night) in 335 patients.[1] For patients without REM during the diagnostic PSG, the authors defined a REM sleep period of > 15 min on the pressure titration as > 10% REM rebound.[1] Using sequential regression modeling, the authors examined eight different thresholds to define REM rebound (10% to 80%), concluding that a REM rebound of 20% exhibited the best model fit (based on Cox and Snell R^2 values).[1]

This definition of REM rebound becomes problematic in patients undergoing split-night PSG (in fact, these patients were excluded from the Brillante study).[1] In a split-night format, one must also take into account the normal predominance of REM in the latter part of the night and the patient-to-patient variability in the duration of the diagnostic portion. In a split-night PSG, there is no clear definition for REM rebound, and perhaps a better definition may compare the percentage of REM sleep during the titration to age-predicted normative values. In our patient, the percentage of REM sleep during the titration study (83% of titration portion, 60% of total night) is clearly above the 15% to 25% value seen in most healthy adults: therefore, we would consider this REM rebound.

PAP initiation is associated with acute transient increases in both slow wave and REM sleep duration. Patients with higher AHI, greater sleep fragmentation, and less REM sleep on diagnostic PSG may be more likely to demonstrate REM rebound.[1] REM rebound typically wanes within days of PAP therapy initiation. PAP initiation has also been associated with an increase in REM density, the number of eye movements per minute of REM sleep.[1,2]

REM sleep can be affected by depression, antidepressant use, and antidepressant withdrawal. Patients with major depression commonly exhibit reduced slow wave sleep duration, reduced REM sleep latency, and increased REM sleep duration. Most antidepressants, including tricyclics, selective serotonin reuptake inhibitors (SSRI), and monoamine oxidase inhibitors, reduce REM sleep duration**.** The abrupt withdrawal of SSRIs, is associated with reduced REM sleep latency and increased REM sleep duration that typically normalize after several days.[3] Bupropion is unique among the antidepressants with effects on REM that are not entirely predictable. Bupropion tends to delay REM onset, but it does not appear to decrease the overall amount of REM sleep like other antidepressants.[4,5] Data conflict on whether bupropion increases overall REM time, or only the duration of the first REM period**.**[4,5]

Our patient later confided that she ran out of sertraline 2 days prior to the PSG, but continued to take bupropion.

SLEEP MEDICINE PEARLS

1. REM rebound is a phenomenon of increased REM activity that can be seen in a variety of clinical scenarios including sleep deprivation, PAP initiation, and withdrawal of REM-suppressing drugs.
2. A proposed definition for clinically significant REM rebound in the context of PAP initiation is a 20% increase in REM duration (in minutes) between pressure titration and diagnostic PSG, as a percentage of the diagnostic PSG REM duration. No clear definition exists for split-night PSG.

Table 1—Factors that may affect REM sleep.

ENHANCE REM		SUPPRESS REM	
Shorten REM latency	**Increase REM time**	**Increase REM latency**	**Decrease REM time**
Sleep deprivation Narcolepsy Withdrawal of REM suppressants PAP initiation	Sleep deprivation Narcolepsy AEDs: gabapentin +/-Bupropion Withdrawal of REM suppressants PAP initiation	Bupropion SSRIs Alcohol and opiates (acute)	AEDs: carbamazepine, phenobarbital, phenytoin SSRIs Cocaine, alcohol, and cannabis (acute) Opiates (acute and chronic)

Steiger 2010, J Psychiatric Research; Brillante 2012, Respirology; Jain 2014, Epilepsia; Ott 2004, J Neuropsychopharm; Angarita 2016, Addic Sci & Clin Practice.

3. In patients demonstrating exaggerated REM sleep activity, a multifactorial etiology with possible cumulative effect should be considered.
4. When REM rebound is observed, patients should be asked about initiation or discontinuation of medications with known REM effects.

CITATION

Palen BN, Donovan LM, Parsons EC. An unexpected polysomnogram finding. *J Clin Sleep Med* 2016;12(11):1567–1569.

ABBREVIATIONS

AED, antiepileptic drug
AHI, apnea-hypopnea index
EEG, electroencephalography
PAP, positive airway pressure
PSG, polysomnography
REM, rapid eye movement
SSRI, selective serotonin reuptake inhibitor

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2016
Submitted in final revised form August, 2016
Accepted for publication August, 2016
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The views expressed in this article are those of the authors and do not reflect the views or policies of the Department of Veterans Affairs.