REM Behavior Disorder Secondary to Antidepressants

Usman Riaz, MD; Jacob Gohari, MD; and Syed Ali Riaz, MD

Rapid eye movement (REM) behavioral disorder (RBD) is a parasomnia characterized by dream-enactment behaviors that emerge due to REM sleep without atonia and can be clinically diagnosed and further confirmed with an overnight sleep study test. The dream content is often recalled at the time of awakening and is typically unpleasant (eg, punching, choking, running into a wall, being attacked or chased, arguing with someone, falling off a cliff), and the person is alert and oriented afterward. The prevalence of RBD is 0.38% to 0.5% of the general population, with a predilection for males.[1,2] RBD usually presents after age 50 years, although any age group can be affected.[3]

RBD may be idiopathic or secondary. At this time, it is unknown if idiopathic RBD (IRBD) truly exists or if it is merely cryptogenic because Lewy bodies were demonstrated by autopsy in two cases of presumptive IRBD.[4-6] Secondary RBD can be related to neurodegenerative disorders, other neurologic disorders, sleep disorders, or medications. Antidepressant medications are one of the secondary causes of RBD, with symptoms of dream enactment occurring in up to 6% of patients who are prescribed antidepressants.[7-9] An acute form of RBD may develop during withdrawal from alcohol or sedative-hypnotic drugs. Medication- or alcohol/drug-induced RBD are possibly reversible by stopping the offending agent.

It is important to keep RBD in mind when prescribing serotonin-modulator medications to patients, as untreated RBD may affect patients' functionality in multiple aspects of life and, further, is a safety risk factor for patients and their bed partner. In fact, between 33% and 65% of patients with RBD have been reported to have had a sleep-related injury to self or their bed partner.[10,11] Moreover, because RBD is associated with and may predate Parkinson's disease and other neurodegenerative disorders, it is important to screen for and monitor patients with RBD longitudinally.[12,13] As such, RBD is a disorder that must be screened for in all patients taking antidepressants and patients with sleep disturbances. In this case report, we present a patient with fluoxetine-induced RBD.

CASE

A 62-year-old female patient with a known past diagnosis of bipolar 1 disorder in remission was transferred to the authors for continuity of psychiatric care. On her initial visit, the patient was taking valproic acid extended-release (1,500 mg nightly) and fluoxetine (20 mg daily) as prescribed by her previous mental health provider. She was referred to the authors because her previous provider stopped accepting her medical health insurance (valproic acid level was 65 µg/mL at the time of referral to the authors).

At follow-up visits with the authors, the patient reported multiple episodes of acting out behaviors in her dreams, usually during the latter part of night, which were distressing to her mood. As per the patient, she had started to notice those symptoms shortly after the addition of fluoxetine 20 mg daily to address her bipolar-associated anxiety symptoms around 4 months ago. After careful review of her previous chart, it was evident that the addition of fluoxetine instead of considering an alternative psychotropic to address her anxiety symptoms was primarily based on the previous provider's clinical preference.

The patient reported multiple episodes of awakening with broken things next to her secondary to possibly acting-out behavior in her dreams. Because the patient had only begun experiencing

From Montefiore Hospital, Albert Einstein College of Medicine, Bronx, New York (UR); Creedmoor Psychiatric Center, Queens Village, New York (JG); and Virtua Health, New Jersey (SAR).

Address correspondence to Usman Riaz, MD, Montefiore Hospital, Division of Substance Abuse, 1510 Waters Place, Bronx, NY 10461; email: usmansyedriaz@gmail.com.

Disclosure: The authors have no relevant financial relationships to disclose.

doi:10.3928/00485713-20211108-01

these issues soon after adding fluoxetine, the problem seemed likely to be associated with fluoxetine in her case, but this was not confirmed pending thorough testing at that time.[8,14] The patient's sleep study results were diagnostic of RBD. The results of the sleep study and the patient's clinical symptoms of acting-out behavior in dreams confirmed the diagnosis of RBD.

In this case, considering the benefits versus risks of medication, the patient's fluoxetine dose of 20 mg was gradually reduced to 10 mg without much improvement in symptoms and was later discontinued. The discontinuation of fluoxetine resulted in a significant improvement in the patient's symptoms of RBD. There is little evidence in the literature or the authors' clinical practice of a dose-response link between antidepressants and RBD. The authors switched the patient to hydroxyzine 50 mg three times a day to address her bipolar anxiety symptoms, and her anxiety symptoms seemed to remain in control with no recurrence of RBD symptoms.

DIAGNOSIS OF RBD

According the third edition of the *International Classification of Sleep Disorders* (ICSD-3),[15] a diagnosis of RBD requires all of the following:

1. Repeated episodes of sleep-related vocalization and/or complex motor behaviors,
2. Behaviors documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep,
3. Presence of REM sleep without atonia (RSWA) on polysomnography,
4. Absence of epileptiform activity during REM sleep, unless RBD can be clearly distinguished from any concurrent REM sleep-related seizure disorder,
5. The sleep disturbance is not better explained by another sleep disorder, a medical or neurologic disorder, a mental disorder, medication use, or a substance use disorder,
6. In-laboratory video polysomnography can exclude other sleep disorders, quantify REM atonia, and capture dream-enactment behaviors, confirming the diagnosis, and
7. Polysomnography may or may not capture a motor event but commonly demonstrates abnormal sustained or phasic muscle activity during REM sleep, as measured by chin or limb electromyography. Polysomnography is also helpful in excluding other sleep-disrupting conditions (eg, obstructive sleep apnea, nocturnal seizures, periodic limb movements).[15]

Differential Diagnoses to Be Considered when Suspecting RBD

The most common disorders to be distinguished from RBD are the non-REM (NREM) parasomnias.

Confusional arousals sleepwalking/sleep terrors. Unlike RBD, NREM parasomnias usually occur in childhood. Additional aspects of the history are helpful in distinguishing NREM parasomnias from RBD.

RBD consists of brief dream enactment (less than 60 seconds) occurring in the latter half of the sleep period, followed by alertness and orientation upon awakening. This presentation contrasts with sleepwalking, in which there is often a lifelong history of prolonged, amnestic, complex, nonviolent activities emanating from the first half of the sleep period. Similarly, confusional arousals are more prolonged (more than 60 seconds) and more often occur in the first half of the night.

Patients who sleepwalk are difficult to awaken and only rarely report dream mentation. In contrast, patients with RBD often recall dream content if awakened and are alert and oriented afterward. This patient's case history was not suggestive of confessional arousal, which was confirmed by sleep study results.

Nightmares. Unlike RBD, nightmares are not associated with motor activity or sleep-related injury. In fact, nightmares are often characterized by sleep paralysis, an inability to move, defend oneself, or scream, which was not the case in this patient.

Obstructive sleep apnea. Behaviors that may mimic RBD can occur when REM sleep is fragmented by obstructive sleep apnea. However, these parasomnia-like behaviors resolve once the sleep-disordered breathing is effectively treated. This phenomenon has been referred to as "pseudo-RBD." In this patient's case, sleep study results ruled out sleep apnea as a cause of RBD.

Periodic limb movement. Unlike RBD, periodic limb movements occur primarily during NREM sleep, are periodic, and are unrelated to dream mentation. Rare cases of frequent and vigorous periodic limb movements during both NREM and REM sleep, mimicking RBD, have been described. In this patient's case, sleep study results ruled out periodic limb movement as a differential diagnosis.

Nocturnal frontal lobe epilepsy. RBD is occasionally confused with nocturnal frontal lobe epilepsy (NFLE). NFLE is characterized by stereotyped, recurrent (ie, up to 20 times episodes per night), abnormal behaviors. Electroencephalography may (but not universally) reveal epileptic activity. Compared with those with RBD, patients with NFLE are younger (typically adolescents) and fully unaware of their nighttime behaviors. It seems that a negative electroencephalography would not rule out NFLE; therefore, it should still be included as a differential diagnosis.

PATHOPHYSIOLOGY OF RBD

The lateral dorsal tegmentum/pedunculopontine tegmentum area in the

brain, which is the site of acetylcholine production, is responsible for REM sleep. Activity of acetylcholine is high during REM, whereas serotonin, histamine, and norepinephrine activity are decreased. Laterodorsal tegmentum/pedunculopontine tegmentum inhibits motor neurons (glycine) and results in atonia/paralysis. An inhibitory brain chemical called glycine is responsible for actively suppressing muscle twitches in REM sleep. Deficiency in glycine levels in the brain cells or inhibition of glycine that controls muscles (motor neurons) were found to cause the violent muscle contractions that mimic the primary symptoms of RBD.[16] The normal physiologic suppression of motor activity during REM sleep is the cumulative result of multiple neuronal circuits that predominantly originate in the pons and ultimately terminate on spinal cord motor neurons.

RBD is the clinical manifestation of a variety of central nervous system pathologies, all of which result in a failure to inhibit spinal motoneurons. These include alpha-synuclein and other forms of neurodegeneration, orexin deficiency (narcolepsy), structural pontine lesions, and toxic effects from medications. In both spontaneous and medication-induced RBD, the loss of REM sleep atonia appears to be related to dysfunction of pontine "REM-on" nuclei in the preceruleus and sublateral dorsal pons and "REM-off" nuclei in the ventral lateral portion of the periaqueductal grey matter and lateral pontine tegmentum.[17,18] The exact mechanism of toxic RBD associated with antidepressants is unknown but likely relates to serotonergic effects. The serotonergic raphe nuclei in the pons have an activating effect on the REM-off nuclei, suggesting a plausible pathological mechanism.[17] Recent findings suggest that a decrease in striatal dopamine transporters may be causally linked to the symptoms of RBD.[19]

RBD AND NEURODEGENERATION

Most patients with spontaneous RBD eventually develop either Parkinson's disease or another disorder of alpha-synuclein neurodegeneration.

Synucleinopathies (also called alpha-synucleinopathies) are neurodegenerative diseases characterized by the abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers, or glial cells. There are three main types of synucleinopathy: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. RBD is common in synucleinopathy, with prevalence ranging from 60% to 90% but not as prevalent in tauopathy (3% to 11%).[20] Tauopathies are clinically, biochemically, and morphologically heterogeneous neurodegenerative diseases characterized by the deposition of abnormal tau (tubulin-associated unit), also called microtubule-associated protein tau, in the brain, which can lead to disease associated with pathological accumulations of tau protein. These accumulations can form neurofibrillary tangles, such as in Alzheimer's disease.

The conversion rate of RBD to to Parkinson's disease is approximately 50% every decade, with a mean interval between RBD onset and emergence of Parkinson's disease of 12.7 years.[20] The presence of anosmia, constipation, and orthostasis increases the likelihood of earlier conversion.

Although patients with antidepressant-associated RBD have a lower risk of neurodegeneration than patients with purely idiopathic RBD, markers of prodromal neurodegeneration are still clearly present. Development of RBD with antidepressants can be an early signal of an underlying neurodegenerative disease. A recent population study showed an increased risk ratio of taking antidepressants for patients with early-onset RBD;[21] furthermore, a study evaluating the effect of selective serotonin reuptake inhibitor (SSRI) medications on motor tone in REM sleep (which specifically excluded patients with RBD) demonstrated that SSRI medications can induce RSWA.[8,17,22-24]

RSWA is not same as RBD unless associated with clinical signs and symptoms, but it is clearly is a predictor of RBD. Although patients with antidepressant-associated RBD have a lower risk of neurodegeneration than those not taking antidepressants, markers of prodromal neurodegeneration are still present. This suggests that antidepressants predominantly trigger clinical presentation of a previously subclinical loss of REM sleep atonia due to an underlying synucleinopathy. Among sleep centers already treating patients with RBD, patients taking antidepressants might be advised that their risk of neurodegenerative disease is lower than in other RBD patients (possibly because antidepressants triggered earlier clinical presentation of their prodromal disease). Nevertheless, clinical follow up is still warranted, given that a neurodegenerative etiology for their symptoms may still be present.[14]

TREATMENT GUIDELINES FOR RBD

The Board of Directors of the American Academy of Sleep Medicine (AASM) approved the following treatment guideline recommendations. All members of the AASM Standards of Practice Committee and Board of Directors completed detailed conflict-of-interest statements and were found to have no conflicts of interest with regard to this subject. There were a number of reviews but no evidence-based treatment recommendations have been published. To address this issue, the Standards of Practice Committee of the AASM commissioned a task force to assess the literature on the treatment of RBD. The task force found that although the literature is voluminous, much of the data are low-level studies, mostly case series and case reports with no randomized, controlled

clinical trials. These studies were deemed insufficient to support the standards or guidelines of a practice parameter. Thus, the Board of Directors authorized the task force to draft a Best Practice Guide on the treatment of RBD based on a systematic review and compilation of recommended evaluation or management strategies.[25–27]

Level A (Recommended)

Modifying the sleep environment is recommended for the treatment of patients with RBD who have sleep-related injury. Frequency of dream-enactment behaviors is not predictive of injury, so all patients with RBD and their bed partners should be counseled on modifying the sleeping environment to prevent injury. For patients with mild symptoms, this may be all that is needed.

Firearms should not be accessible, and sharp or easily breakable items (eg, lamps) should be removed from the immediate sleeping area. In the event of continued vigorous behaviors, sleeping alone is advised. Many patients resort to using padded bed rails or sleeping in a sleeping bag. Other novel strategies are in development. Exiting the bed while acting out a dream is a high-risk behavior that may result in traumatic injury. A bed alarm that delivers a customized calming message at the onset of dream enactment can prevent a patient from exiting the bed and avert sleep-related injury.

Level B (Suggested)

Melatonin. Melatonin is the preferred first-line therapy in patients with frequent, disruptive, or injurious behaviors. It is generally preferred as the initial therapy for RBD based on its favorable side effect profile.[28-30] It tends to be better tolerated than the alternative first-line therapy (clonazepam), with fewer reported falls and injuries compared with treatment with clonazepam.[31] The dose of melatonin required to suppress behaviors in patients with RBD varies. Most patients achieve significant improvement with doses ranging from 6 to 18 mg nightly.[32-34] In the author's clinical practice, melatonin is initiated with a starting dose of 3 mg at night and increased in 3-mg increments until the disruptive and injurious behaviors have ceased. Melatonin tends to be well tolerated at these doses, with occasional patients developing dose-limiting gastrointestinal distress or headaches. Other reported side effects are usually mild and include sleepiness, fatigue, dizziness, unsteadiness, and cognitive alteration. Melatonin undergoes hepatic metabolism and should be used with caution in patients with hepatic impairment. Behaviors typically return when melatonin is reduced or discontinued, and most patients require lifelong therapy. If behaviors are inadequately suppressed with melatonin, low-dose clonazepam is an effective add-on or alternative therapy.

Clonazepam. Clonazepam is suggested for the treatment of RBD but should be used with caution in patients with dementia, gait disorders, or concomitant obstructive sleep apnea. Its use should be monitored carefully over time as RBD appears to be a precursor to neurodegenerative disorders with dementia in some patients. Clonazepam is suggested to decrease the occurrence of sleep-related injury caused by RBD in patients for whom pharmacologic therapy is deemed necessary.[35,36] Low-dose clonazepam (0.5 to 1 mg at bedtime) has long been recognized as a treatment for RBD. Like melatonin, the therapeutic mechanisms of clonazepam in RBD are not fully understood, although it is thought that clonazepam may reduce the frequency of unpleasant dreams, thus decreasing violent dream enactment behavior.

Although low doses of clonazepam (0.5 to 1 mg at bedtime) are typically sufficient to suppress RBD behaviors, side effects can limit its utility. In a cohort study that included 167 patients treated with clonazepam (mean effective dose 1 mg), 39% of patients reported side effects, most commonly morning sedation and dizziness, leading to drug discontinuation in 9%.[21] Side effects can be particularly problematic among older adults and in the setting of advanced neurodegenerative disease, where clonazepam's prolonged duration of action may result in morning sedation as well as gait and cognitive impairment. In these patients, a lower initial dose (eg, 0.125 or 0.25 mg) and close monitoring for the emergence of toxicity is suggested.

Level C (May Be Considered)

The medications listed in **Table 1** may be considered for treatment of RBD, but evidence is very limited with only a few patients having been studied for each medication.

Treatment of Toxic RBD

Medications known to exacerbate RBD, including SSRIs, serotonin-norepinephrine-reuptake inhibitors, and tricyclic antidepressants, should be discontinued or avoided if possible in patients with RBD. Cases of toxic RBD are likely self-limited following discontinuation of the offending medication. Bupropion has been shown to inhibit the reuptake of dopamine by acting on the striatal dopamine transporter, thereby increasing synaptic dopamine. It has been suggested that, because of its prodopaminergic actions, bupropion may be the antidepressant of choice for treating depression associated with RBD.[37] The literature regarding augmentation with bupropion while taking other antidepressants is deficient, and future studies might be beneficial to address it.

CONCLUSION

Antidepressant medications are one of the secondary causes of RBD, although the exact mechanism is unknown. A

Table 1.

Medications that May Be Considered for Treatment of Rapid Eye Movement Behavioral Disorder

- Pramipexole (efficacy studies have shown contradictory results[39,40])
- Zopiclone[41]
- Benzodiazepines other than clonazepam[42]
- Yi-gan san[43]
- Desipramine[44]
- Clozapine[1]
- Carbamazepine[45]
- Sodium oxybate[46,47]

theory being explored is the serotonergic effect of antidepressants and the loss of REM sleep atonia appear to be related to dysfunction of pontine REM on nuclei in the precercules and sublateral dorsal pons and "REM-off" nuclei in the ventral lateral portion of the periaqueductal grey matter and lateral pontine tegmentum. The serotonergic raphe nuclei in the pons have an activating effect on "REM-off" nuclei, suggesting a plausible pathological mechanism.[17] In clinical practice, it is often difficult to switch patients to alternative antidepressants if the patient's psychiatric symptoms have been stabilized. In the case of the patient presented in this article, valproic acid worked well to address her bipolar 1 disorder and fluoxetine was switched to hydroxyzine without exacerbation of her anxiety symptoms. In patients who are bipolar, the use of antidepressants like fluoxetine is still controversial and the authors were able to justify its discontinuation without exacerbation of mood/anxiety symptoms.

The first-line treatment strategy to address RBD should be to review the patient's antidepressants medications and try to adjust the dosage or switch to alternative antidepressants (eg, bupropion) if circumstances permit, depending on clinical judgment. If psychotropic adjustment is not feasible, safety measures and melatonin and clonazepam are the primary treatment options to address this parasomnia secondary to antidepressants. Antidepressant medications are strongly associated with RSWA even in the absence of RBD symptoms, and future prospective studies analyzing RSWA in patients with and without RBD are necessary to establish the influence of antidepressants and psychiatric disease on RSWA and RBD, to delineate whether antidepressant medications play a mediating role in unveiling RSWA and RBD earlier than it may otherwise appear in predisposed patients, or to determine whether antidepressants instead cause a distinctive and potentially reversible pathophysiology. It is important to stay cognizant of this disorder when starting patients on antidepressant medications because untreated RBD can have severe consequences, including safety concerns and neurodegenerative diseases.[38] Long-term neurological follow up is recommended secondary to the possible association of RBD with neurodegenerative diseases, as markers of prodromal neurodegeneration are still clearly present in patients with RSWA/RBD while they are taking antidepressants.

REFERENCES

1. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. *Brain*. 2000;123(Pt 2):331-339. https://doi.org/10.1093/brain/123.2.331 PMID:10648440
2. Chiu HF, Wing YK, Lam LC, et al. Sleep-related injury in the elderly—an epidemiological study in Hong Kong. *Sleep*. 2000;23(4):513-517. https://doi.org/10.1093/sleep/23.4.1e PMID:10875558
3. Chiu HFK, Wing YK, Chung DWS, Ho CK. REM sleep behaviour disorder in the elderly. *Int J Geriatr Psychiatry*. 1997;12(9):888-891. https://doi.org/10.1002/(SICI)1099-1166(199709)12:9<888::AID-GPS656>3.0.CO;2-N PMID:9309465
4. Uchiyama M, Isse K, Tanaka K, et al. Incidental Lewy body disease in a patient with REM sleep behavior disorder. *Neurology*. 1995;45(4):709-712. https://doi.org/10.1212/WNL.45.4.709 PMID:7723959
5. Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*. 2007;130(Pt 11):2770-2788. https://doi.org/10.1093/brain/awm056 PMID:17412731
6. Mahowald MW, Schenck CH, Bornemann MAC. Pathophysiologic mechanisms in REM sleep behavior disorder. *Curr Neurol Neurosci Rep*. 2007;7(2):167-172. https://doi.org/10.1007/s11910-007-0013-7 PMID:17355839
7. Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: literature review, qualitative scoring, and comparative analysis. *J Clin Sleep Med*. 2010;6(1):79-83. https://doi.org/10.5664/jcsm.27716 PMID:20191944
8. Teman PT, Tippmann-Peikert M, Silber MH, Slocumb NL, Auger RR. Idiopathic rapid-eye-movement sleep disorder: associations with antidepressants, psychiatric diagnoses, and other factors, in relation to age of onset. *Sleep Med*. 2009;10(1):60-65. https://doi.org/10.1016/j.sleep.2007.11.019 PMID:18226952
9. Lam SP, Fong SY, Ho CK, Yu MW, Wing YK. Parasomnia among psychiatric outpatients: a clinical, epidemiologic, cross-sectional study. *J Clin Psychiatry*. 2008;69(9):1374-1382. https://doi.org/10.4088/JCP.v69n0904 PMID:19193338
10. Comella CL, Nardine TM, Diederich NJ, Stebbins GT. Sleep-related violence, injury, and REM sleep behavior disorder in Parkinson's disease. *Neurology*. 1998;51(2):526-529. https://doi.org/10.1212/WNL.51.2.526 PMID:9710029

11. Ohayon MM, Caulet M, Priest RG. Violent behavior during sleep. *J Clin Psychiatry*. 1997;58(8):369-376. https://doi.org/10.4088/JCP.v58n0808 PMID:9515980
12. Schenck CH, Boeve BF, Mahowald MW. Delayed emergence of a parkinsonian disorder or dementia in 81% of older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder: a 16-year update on a previously reported series. *Sleep Med*. 2013;14(8):744-748. https://doi.org/10.1016/j.sleep.2012.10.009 PMID:23347909
13. Iranzo A, Fernández-Arcos A, Tolosa E, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. *PLoS One*. 2014;9(2):e89741. https://doi.org/10.1371/journal.pone.0089741 PMID:24587002
14. Postuma RB, Gagnon J-F, Tuineaig M, et al. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? *Sleep*. 2013;36(11):1579-1585. https://doi.org/10.5665/sleep.3102 PMID:24179289
15. Sateia MJ. International Classification of Sleep Disorders-third edition: highlights and modifications. *Chest*. 2014 Nov;146(5):1387-1394. doi: 10.1378/chest.14-0970. PMID: 25367475.
17. Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci*. 2010;1184(1):15-54. https://doi.org/10.1111/j.1749-6632.2009.05115.x PMID:20146689
18. Boeve BF. Predicting the future in idiopathic rapid-eye movement sleep behaviour disorder. *Lancet Neurol*. 2010;9(11):1040-1042. https://doi.org/10.1016/S1474-4422(10)70221-0 PMID:20869916
19. Eisensehr I, Linke R, Tatsch K, et al. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. *Sleep*. 2003;26(5):507-512. doi:10.1093/SLEEP/26.5.507 PMID:12938802
20. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. *Neurology*. 2009;72(15):1296-1300. https://doi.org/10.1212/01.wnl.0000340980.19702.6e PMID:19109537
21. Fernández-Arcos A, Iranzo A, Serradell M, Gaig C, Santamaria J. The clinical phenotype of idiopathic rapid eye movement sleep behavior disorder at presentation: a study in 203 consecutive patients. *Sleep*. 2016;39(1):121-132. https://doi.org/10.5665/sleep.5332 PMID:26940460
22. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. *Sleep*. 2004;27(2):317-321. https://doi.org/10.1093/sleep/27.2.317 PMID:15124729
23. Iranzo A, Santamaria J. Bisoprolol-induced rapid eye movement sleep behavior disorder. *Am J Med*. 1999;107(4):390-392. https://doi.org/10.1016/S0002-9343(99)00245-4 PMID:10527042
24. Postuma RG, Gagnon J-F, Tuineaig M, Bertrand J-A, Latreille, V, Desjardins, C, Montplaisir, JY. Antidepressants and REM sleep behavior disorder: isolated side effect or neurodegenerative signal? *Sleep*. 2013;36(11):1579-1585. https://doi.org/10.5665/sleep.3102 PMID: 24179289
25. Aurora RN, Zak RS, Maganti RK, et al; Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med*. 2010;6(1):85-95. https://doi.org/10.5664/jcsm.27717 PMID:20191945
26. Phillips B, Ball C, Sackett D, et al. Levels of evidence. Oxford Centre for Evidence-Based Medicine. March 2009. Accessed November 16, 2021. https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009
27. Fitch K, Bernstein SJ, Aguilar MD, et al., eds. *The RAND/UCLA Appropriateness Method User's Manual*. Rand Corporation; 2001. https://www.rand.org/pubs/monograph_reports/MR1269.html
28. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation. *Mov Disord*. 1999;14(3):507-511. https://doi.org/10.1002/1531-8257(199905)14:3<507::AID-MDS1021>3.0.CO;2-8 PMID:10348479
29. Takeuchi N, Uchimura N, Hashizume Y, et al. Melatonin therapy for REM sleep behavior disorder. *Psychiatry Clin Neurosci*. 2001;55(3):267-269. https://doi.org/10.1046/j.1440-1819.2001.00854.x PMID:11422870
30. McGrane IR, Leung JG, St Louis EK, Boeve BF. Melatonin therapy for REM sleep behavior disorder: a critical review of evidence. *Sleep Med*. 2015;16(1):19-26. https://doi.org/10.1016/j.sleep.2014.09.011 PMID:25454845
31. McCarter SJ, Boswell CL, St Louis EK, et al. Treatment outcomes in REM sleep behavior disorder. *Sleep Med*. 2013;14(3):237-242. https://doi.org/10.1016/j.sleep.2012.09.018 PMID:23352028
32. McGrane IR, Leung JG, St Louis EK, Boeve BF. Melatonin therapy for REM sleep behavior disorder: a critical review of evidence. *Sleep Med*. 2015;16(1):19-26. https://doi.org/10.1016/j.sleep.2014.09.011 PMID:25454845
33. Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med*. 2003;4(4):281-284. https://doi.org/10.1016/S1389-9457(03)00072-8 PMID:14592300
34. Kunz D, Mahlberg R. A two-part, double-blind, placebo-controlled trial of exogenous melatonin in REM sleep behaviour disorder. *J Sleep Res*. 2010;19(4):591-596. https://doi.org/10.1111/j.1365-2869.2010.00848.x PMID:20561180
35. Wing YK, Lam SP, Li SX, et al. REM sleep behaviour disorder in Hong Kong Chinese: clinical outcome and gender comparison. *J Neurol Neurosurg Psychiatry*. 2008;79(12):1415-1416. https://doi.org/10.1136/jnnp.2008.155374

PMID:19010959

36. Culebras A, Moore JT. Magnetic resonance findings in REM sleep behavior disorder. *Neurology*. 1989;39(11):1519-1523. https://doi.org/10.1212/WNL.39.11.1519 PMID:2812333
37. Quan SF. The Journal of Clinical Sleep Medicine–a decade of progress: looking backward and forward. *J Clin Sleep Med*. 2014;10(1):5-6. https://doi.org/10.5664/jcsm.3344
38. Schenck CH, Mahowald MW. Rapid eye movement sleep parasomnias. *Neurol Clin*. 2005;23(4):1107-1126. https://doi.org/10.1016/j.ncl.2005.06.002 PMID:16243618
39. Fantini ML, Gagnon J-F, Filipini D, Montplaisir J. The effects of pramipexole in REM sleep behavior disorder. *Neurology*. 2003;61(10):1418-1420. https://doi.org/10.1212/WNL.61.10.1418 PMID:14638967
40. Schmidt MH, Koshal VB, Schmidt HS. Use of pramipexole in REM sleep behavior disorder: results from a case series. *Sleep Med*. 2006;7(5):418-423. https://doi.org/10.1016/j.sleep.2006.03.018 PMID:16815751
41. Bonakis A, Howard RS, Williams A. Narcolepsy presenting as REM sleep behaviour disorder. *Clin Neurol Neurosurg*. 2008;110(5):518-520. https://doi.org/10.1016/j.clineuro.2008.01.015 PMID:18343568
42. Anderson KN, Shneerson JM. Drug treatment of REM sleep behavior disorder: the use of drug therapies other than clonazepam. *J Clin Sleep Med*. 2009;5(3):235-239. https://doi.org/10.5664/jcsm.27492 PMID:19960644
43. Shinno H, Kamei M, Nakamura Y, Inami Y, Horiguchi J. Successful treatment with Yi-Gan San for rapid eye movement sleep behavior disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(7):1749-1751. https://doi.org/10.1016/j.pnpbp.2008.06.015 PMID:18656519
44. Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. *Sleep*. 1986;9(2):293-308. https://doi.org/10.1093/sleep/9.2.293 PMID:3505730
45. Bamford CR. Carbamazepine in REM sleep behavior disorder. *Sleep*. 1993;16(1):33-34. PMID:8456232
46. Moghadam KK, Pizza F, Primavera A, Ferri R, Plazzi G. Sodium oxybate for idiopathic REM sleep behavior disorder: a report on two patients. *Sleep Med*. 2017;32:16-21. https://doi.org/10.1016/j.sleep.2016.04.014 PMID:28366329
47. Shneerson JM. Successful treatment of REM sleep behavior disorder with sodium oxybate. *Clin Neuropharmacol*. 2009;32(3):158-159. https://doi.org/10.1097/WNF.0b013e318193e394 PMID:19483483