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COMMENTARY

Ramelteon for Idiopathic REM Sleep Behavior Disorder: Implications for Pathophysiology and Future Treatment Trials

Commentary on Esaki et al. An open-labeled trial of ramelteon in idiopathic rapid eye movement sleep behavior disorder. *J Clin Sleep Med* 2016;12(5):689–693.

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Idiopathic REM sleep behavior disorder (iRBD) is a common injurious parasomnia, with a prevalence of 1% to 7% in the general population that is highest in older adults.[1–3] Due to the nature of often violent, nightmarish dream content, patients may inadvertently punch or kick their bedpartner, or fall or leap from bed, leading to injury.[4–6] While there are no current population based estimates of injurious RBD episodes, our recent survey based study demonstrated that approximately 55% of RBD patients reported at least mild injury prior to treatment, and up to 11.7% reported serious injuries including fractures and subdural hematomas.[5] Thus, early introduction of an efficacious treatment that may prevent injury in RBD is an imperative.

Traditional treatments options for RBD have been clonazepam and melatonin.[4–12] Clonazepam has been favored by most clinicians as initial RBD therapy with large retrospective case series reports suggesting that approximately 80% or more of RBD patients treated with clonazepam had control of dream enactment behaviors (DEB). However, one recent study found that clonazepam did not significantly reduce injurious DEB,[11] and a new prospective study found that only 66.7% of patients had injurious parasomnia behaviors controlled by clonazepam.[13] Several reports have found that melatonin may be as (or more) effective than clonazepam, and that melatonin is better tolerated by RBD patients who are frequently elderly and vulnerable to adverse effects of drowsiness, dizziness, imbalance, and sexual dysfunction, which are common with clonazepam.[10–12] However, a concern with melatonin in the United States limiting enthusiasm for melatonin is its sole availability as an over the counter, unregulated homeopathic/naturopathic agent, reducing clinicians' confidence in consistent drug bioavailability, efficacy, and safety.[12] In Europe, melatonin is instead marketed as a sustained release regulated product, (Circadin; Neurim Pharmaceuticals, Tel Aviv, Israel) , which is approved for treatment of insomnia in the European Union. However, to date, melatonin treatment for RBD by European sleep centers seems to remain relatively limited, and to our knowledge, there have been no systematic efficacy studies of the branded EU formulation Circadin for RBD therapy.

Ramelteon (Rozerem) is an attractive alternative to melatonin since it exerts melatonergic agonism in a reliable formulation. Ramelteon is a selective MT1 and MT2 agonist (with minimal to no MT3 binding) that is approved for the treatment of insomnia in the United States and is available in several countries worldwide.[14–16] Advantages of ramelteon include a reliable marketed formulation, rapid efficacy, an objective evidence basis for use, limited abuse potential, and lack of rebound or withdrawal insomnia upon drug cessation.[17] Interestingly, a recent study also found that ramelteon was beneficial for preventing delirium in hospitalized medical inpatients.[18] The most frequent adverse effects of ramelteon are somnolence, dizziness, nausea, fatigue, and headache.[14–17] Disadvantages of ramelteon include its comparative expense to melatonin in the United States, and several possible drug-drug interactions, including reduced ramelteon serum concentrations when given in combination with potent cytochrome P450 enzyme inducers such as rifampin, while certain cytochrome enzyme inhibitors such as ketoconazole and asfluconazole may instead raise ramelteon concentrations. Ramelteon may also interact with amiodarone, ciprofloxacin, fluvoxamine, and ticlopidine. Ramelteon is metabolized to an active metabolite M-II, which also has weak binding to the serotonin 5-HT2B receptor. There have been no published comparative studies between melatonin and ramelteon thus far, to our knowledge. There has been one previous report of ramelteon use in RBD, which reduced injurious dream enactment behaviors in two patients with symptomatic RBD (in one Parkinson disease patient and in one multiple system atrophy patient).[19]

In this issue of the *Journal of Clinical Sleep Medicine*, Esaki and colleagues describe a pilot open-label treatment trial of ramelteon 8 mg in 12 iRBD patients (8 men, mean age 70.9 years) over a 4-week period, analyzing both subjectively rated dream enactment behavior (DEB) frequency-severity on a visual analog scale (VAS), as well as objective polysomnographic DEBs rated on the RBD severity scale, and quantitative measures of REM sleep without atonia (RSWA).[20] Two subjects dropped out due to allergic rash or dizziness, leaving 10 evaluable patients. They found that 7 of the 10 remaining patients improved only on the caregiver-rated VAS, 3 patients did not respond and worsened on the VAS, and that treatment in the remaining 10 patients was generally well tolerated. However, there was

no significant overall impact of ramelteon treatment on clinical dream enactment, video-PSG rated RBD behavior severity, or RSWA measures (which in fact showed increases in RSWA in 6 of the 10 patients). Interestingly, 4 of the 6 patients whose RSWA measures increased still reported improvement in DEB VAS ratings. While limited by usual biases inherent in open-label treatment trials, and underpowered to detect significant change in DEB, these findings expand data on available treatment alternatives for RBD, and provide an effect size to enable future definitive randomized controlled trials of ramelteon in RBD. The data also raise interesting questions about what really matters in RBD treatment, subjective or objective outcomes, and by what mechanism(s) pharmacologic agents may exert therapeutic effects in RBD treatment.

Ramelteon showed a trend toward benefiting subjective clinical DEBs, even in patients whose RSWA worsened, and produced no objective changes in DEBs in these iRBD patients, suggesting it may be ineffective in RBD treatment. Concerningly, two of the initial 12 patients dropped out due to drug allergy or intolerable adverse effects. A future appropriately powered and blinded trial will be necessary to determine if ramelteon is safe, tolerable, and effective in RBD treatment.

Ramelteon, like clonazepam as found in another recent treatment trial of RBD,[13] appears to influence the subjectively determined frequency of DEBs but has no impact on objective RSWA metrics or objective DEBs during PSG, suggesting a possible dissociation between subjective clinical benefit and RSWA pathophysiology. Agents such as clonazepam and melatonergic drugs[10–12,21] may have their impact primarily on cortical and subcortical neural networks that mediate dreaming and/or facilitate cortically and subcortically generated movements, instead of acting primarily upon lower pontomedullary REM atonia control centers that are functionally impaired in RBD and lead to the permissive RSWA pathophysiology. Attractive targets for exerting therapeutic effects of ramelteon and clonazepam may be the neural networks that mediate dreaming, and/or "top down" cortically or subcortically generated sleep-related movements.[22–24]

Evidence for dissociation between pharmacologically mediated improvement in dream mentation and accompanying DEBs without impact upon RSWA pathophysiology has intriguing implications for RBD pathophysiology. RBD has been thought to primarily involve loss of REM atonia control, leading to permissive release of motor activity during dreaming in REM sleep.[1,4,25] A more recent "bottom up" interpretation has also suggested that RBD patients may be "dreaming out their acts" rather than "acting out their dreams"; that is, a "bottom-up" pathophysiology suggests that cortically generated dream mentation may be a reactive phenomenon to a primary downstream brainstem or peripherally generated movement, that facilitates expression of characteristically violent RBD dream mentation.[25] Brainstem generation of typical "enactment" type complex movements of defensive postures and complex motor behaviors is certainly plausible, given that rats and monkeys may show similar complex behaviors following brainstem stimulation alone.[25] However, pontomedullary and/or peripheral dysfunction and movement with secondary "reactive" dream mentation ("dreaming out of acts") may not fully explain nonviolent complex motor behaviors seen in RBD patients, nor does this model explain why patients with isolated/incidental RSWA (a relatively common polysomnographic finding seen in approximately 25% of normal community adults,[26] especially older men [i.e., the highest risk demographic for incident RBD]),[27] do not also commonly exhibit overt DEBs and develop clinical RBD. Longitudinal followup suggests that only 7% to 14% of isolated/incidental RSWA patients develop DEB with "full blown" RBD,[28] and if the "bottom up" explanation for DEBs is the sole mechanism operating in RBD, one might expect that all patients having the permissive state of RSWA would commonly manifest DEBs. Moreover, these two potential mechanisms involving "top-down" and "bottom-up" influences underlying complex motor behaviors in RBD may not be mutually exclusive; rather, each may serve as a feed-forward influence on the other. Any therapy that reduces the influence of either mechanism could reduce overt dream enactment behavior.

The disassociation between pharmacologic efficacy on subjective dream enactment frequency without direct impact on RSWA pathophysiology may suggest that a "dreaming loop" (presumably involving a neural network overlapping in part with the waking default mode network and REM active brain structures, including the dorsal pontine tegmentum, amygdala, limbic, and paralimbic cortices including the medial prefrontal, anterior cingulate, medial basal forebrain, and posterior parieto-occipital cortices)[22–24] are responsible for initiating DEBs seen in RBD, while dysfunction in the lower REM atonia control "RSWA loop" circuitry within the brainstem and spinal cord (i.e., dorsal pontine sublateral dorsal nucleus, medullary nucleus gigantocellularis, alpha motoneurons, and spinal interneurons) is only a permissive condition that, under the influence of supratentorial structures, enables overt DEB to occur. Further prospective research studies utilizing multimodality neuroimaging and neurophysiologic techniques will be necessary to fully characterize the responsible cortical and subcortical structures facilitating the enigmatic dream mentation and actual DEB in RBD patients, and upon which neural substrates pharmacologic treatments may act to reduce unpleasant nightmares and injurious behaviors in RBD. Randomized controlled trials will be necessary to establish an adequate evidence basis for the efficacy and safety of RBD treatments.

CITATION

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