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Editorial

Clinical trials in REM sleep behavior disorder: an urgent need for better evidence☆

Few topics in sleep medicine have gathered more interest than that of REM sleep behavior disorder (RBD). Although RBD was first clinically reported over 30 years ago [1], little progress has been made in the area of therapeutics for this condition. Currently, clonazepam and melatonin continue to be the two most commonly recommended treatments, despite the fact that supporting evidence for clonazepam is limited to case series and open label studies. A seminal randomized placebo-controlled trial (RCT) by Kunz and Mahlberg [2] suggested superiority of melatonin over placebo. The Best Practice Guide issued by the American Academy of Sleep Medicine [3], however made a weak level B recommendation (ie, intervention is suggested) for either drug. Since Kunz and Mahlberg's RCT over eight years ago, only three other controlled trials were published: one trial of memantine in probable RBD [4], and two RCTs supporting the efficacy of transdermal rivastigmine in refractory RBD [5,6]. Most prescribers continue to recommend clonazepam and melatonin to their patients, without further evidence or recommendations.

After waiting nearly a decade, sleep practitioners now have the results of two new RCTs, published separately by two groups of Korean researchers, one evaluating melatonin, the other clonazepam [7,8]. Unfortunately, neither study met their desired primary endpoint. These two trials illustrate the potential challenges in designing therapeutic trials in RBD.

The study by Jun and colleagues [7] evaluated the efficacy of prolonged-release melatonin at doses of 2 mg and 6 mg nightly versus placebo. The authors utilized a four week, double-blind parallel trial design in patients with video polysomnography (vPSG) confirmed idiopathic RBD (ie, without signs of central neurodegeneration). They selected two primary endpoints: the percentage of participants with a self-administered 7-point Clinical Global Impression-Improvement (CGI-I) scale of “very much” or “much improved” in terms of dream-enactment behaviors; and a reduction of the total RBD questionnaire-Honk Kong (RBD-HK) score. In sum, 25 of the 30 participants completed the trial. A per-protocol analysis showed no superiority of any melatonin dose over placebo with either primary endpoint. No objective measures of RBD severity were obtained, and data was self-reported by patients without caregiver report. In each intervention group, over half of participants reported either “no change” or “minimal improvement” in RBD symptoms.

The second trial by Shin and colleagues [8] evaluated the efficacy of clonazepam at a stable dose of 0.5 mg over placebo in probable RBD (without vPSG confirmation) in patients with mild to moderate Parkinson's disease (Hoehn and Yahr stage of 1–3). The authors utilized a four week double-blind randomized trial. The primary outcome was again based on the CGI-I scale, however this study relied on caregivers' responses, who were requested to sleep in the same room and monitor for frequency, severity and character of RBD behaviors. Of the 40 participants enrolled, 37 completed the trial. Although intention-to-treat analysis showed a median result of “much improved” in the clonazepam group, this was not statistically better than placebo. Responder rates were 76% and 65% for clonazepam and placebo, respectively. Baseline RBD severity on the CGI severity scale was lower in the clonazepam group, however, this did not reach statistical significance compared with the placebo group.

Measuring treatment efficacy in RBD is a challenging task, even for the drugs that have been most extensively used and deemed to be effective by patients [9] and prescribers. By definition, RBD only manifests itself during sleep and ranges from minimal and barely noticeable twitches or lip movements without vocalizations, to loud shouting and injurious movements. Almost half of patients remain unaware that they are acting out their dreams [10] while the remaining half will likely underestimate the true frequency of RBD episodes. Caregivers, when present, may only notice the most dramatic behaviors. In fact, a number of patients will come to medical attention only after a violent episode. This advocates for more objective and accurate measures of RBD in the ambulatory setting, not only for screening purposes, but for assessing treatment efficacy in clinical trials.

The Shin study illustrates that a response rate of 65% with placebo leaves little efficacy margin for genuinely more efficacious treatment, and this teaches us that careful selection of efficacy endpoints will be critical in the design of future trials. Although rivastigmine is not as widely prescribed, it is to date the only drug supported by two RCTs [5,6]. Notably, the primary endpoint chosen in these two trials was frequency of RBD episodes reported by caregivers. This speaks to the need for more objective efficacy endpoints, such as home actigraphy and in-lab vPSG quantification of REM without atonia indices. Additionally, these two trials—as well as the other “positive” trial with melatonin by Kunz and Mahlberg — utilized a cross-over design, which may have further increased their power [2].

Finally, effects sizes in these two recent trials may have been dampened or constrained due to various factors relating to protocol. Anecdotal but widely shared clinical experience suggests that the efficacy of clonazepam is dose-dependent, often requiring doses of 0.75 mg and above. While 0.5 mg did not seem to control RBD episodes in a number of trial participants, flexible rather than stable dosing may have led to a more significant benefit. Such a

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dose-response relationship is not known for melatonin. Melatonin is used in RBD at doses ranging from 2 to 12 mg and sometimes higher; such doses are 10-100x greater than endogenous levels. Although a prolonged-release formulation and higher melatonin doses seem compelling in the treatment of insomnia, we currently do not know if immediate-release formulations or lower doses are superior in the treatment of RBD. The other point to remember is mentioned by Kunz in his editorial that melatonin should be taken at the same time each night [11]. In addition, as melatonin has been reported to have an outlasting clinical effect, an adequate washout period should be allowed prior to any baseline measure. It is thus possible that some participants in the study had received melatonin treatment prior to clonazepam—a treatment that may continue to be used first line in the vulnerable patient population affected by Parkinson's disease.

In conclusion, these possibly failed rather than negative trials have taught us several important lessons to take into account when designing the next treatment trial in RBD, lessons which nonetheless can be overcome with careful planning, and will hopefully yield more efficacious data for patients with this common and dangerous condition.

Conflict of interest

All authors report no financial conflicts to declare.

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Emmanuel H. During*, Mitchell G. Miglis
Stanford Center for Sleep Sciences and Medicine
Department of Psychiatry and Behavioral Sciences
Stanford University Medical Center
Redwood City, CA, USA

Department of Neurology & Neurological Sciences
Stanford University
Palo Alto, CA, USA

* Corresponding author. 450 Broadway St., Pavilion B, 2nd Floor, C 5730, Redwood City, CA 94063, USA.
E-mail address: eduring@stanford.edu (E.H. During).

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